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# THE FACTOR OF PREVIOUS TREATMENT IN EXPERIMENTAL MENSTRUATION[1]

DORIS H. PHELPS

*From the Department of Obstetrics & Gynecology, Vanderbilt University School of Medicine, Nashville, Tennessee*

AN EXPERIMENTAL study of the disorders of menstruation has been in progress in our laboratory since 1929. The approach has been along two lines: 1) study of the changes in endometrial histology associated with abnormal uterine bleeding and 2) experimental production of abnormal menstruation in monkeys and direct observation of the associated vascular phenomena. Among other things, the study has demonstrated that menstrual disorders result from lesions in any of the endocrine glands or from constitutional disease secondarily affecting the endocrine system. The primary lesion operates through the ovaries to produce the menstrual symptom. The degree of ovarian involvement is indicated by the endometrial histology. There is no constant correlation between the type of menstrual abnormality and the severity of the ovarian dysfunction as indicated by the endometrium (Burch and collaborators, 1937; 1942 (1, 2)).

The study of endometrial vascular phenomena was undertaken in the hope of clarifying the question of the relationship of the bleeding abnormalities to ovarian failure. This report is one of a series dealing with various aspects of the study.

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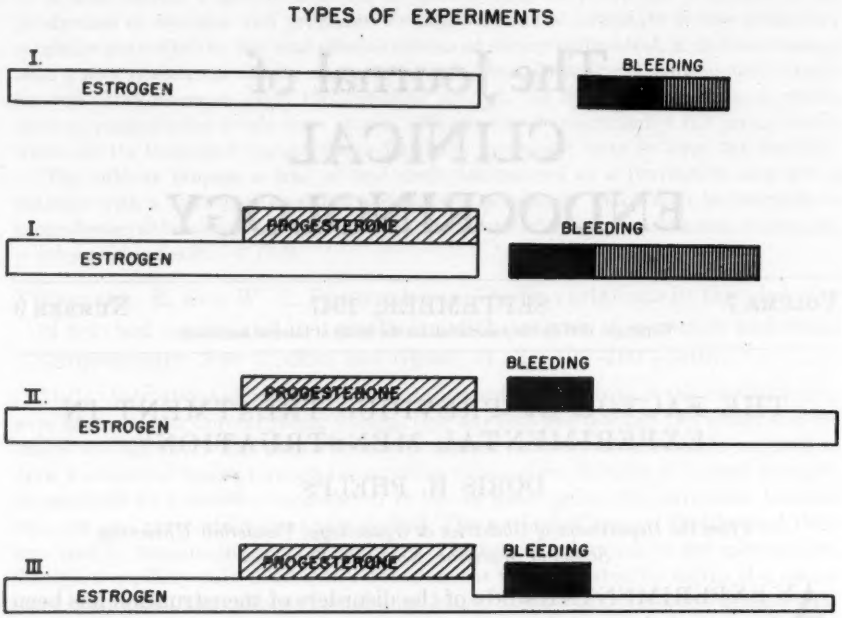


FIG. 1. Types of experimental treatment employed in the present study. Each bar represents one type of treatment. The width of the bar indicates the relative magnitude of the daily dose. The narrow bars indicate dosages within the 'threshold' range (Zuckerman, 1937), the wide bars, dosages above this range. Relative duration of treatment, latent period and uterine bleeding is indicated horizontally. The bars have no specific quantitative significance. The division of bars representing bleeding into black and lined portions is intended to indicate that bleeding produced by the respective types of treatment was sometimes of normal duration, sometimes prolonged.

In a previous report (Phelps, 1946a (5)) evidence was presented which indicates that uterine bleeding is not controlled by any one hormonal influence but by a combination of influences. The factors which may affect any given episode of bleeding can be classified in three categories: 1) the current hormonal stimulus, i.e., the course of stimulation that produces the bleeding, 2) conditions existing prior to application of the current stimulus and 3) the stimulus acting subsequent to the onset of flow.

The factors comprising the first category, the current hormonal stimulus, were discussed in the previous report (Phelps, 1946a (5)). The present report deals with conditions existing prior to application of the current stimulus, the purpose being to present evidence concerning the nature of endocrine factors comprising this category and the mechanism through which their influence upon uterine bleeding is exerted.

The method employed in the study has been described elsewhere (Phelps, 1946 b (6)). Briefly, it consisted of inducing menstruation in ovariectomized rhesus monkeys by injecting ovarian hormones, recording the amount and duration of the uterine bleeding produced and observing the associated vascular phenomena by means of intraocular endometrial transplants (Markee, 1940 (4)). One hundred seven episodes of uterine bleeding were produced in nine monkeys. Hormone dosages employed and duration of treatment varied (cf. table 5). Duration of the interval between courses of treatment varied from 23 to 245 days.

The manner of administering the hormones is indicated in Fig. 1. Data obtained in 52 experiments in which bleeding was precipitated by cessation of treatment (type I, Fig. 1) formed the basis for the present report. In these experiments, no treatment was administered subsequent to the onset of flow.

TABLE 1. EXPERIMENTS OF TYPE I

No treatment subsequent to onset of flow

| Daily Dose | | Days Injected | No. of Experiments | Duration of Bleeding, Days |
|---|---|---|---|---|
| Estrogen, I. U. | Progesterone, mg. | | | |
| 500 | 1 or 2 | 28 | 22 | 4–50 |
| 1250 | 1 | 28–39 | 6 | 3–18 |
| 1250 | ¼ | 42–44 | 7 | 6–18 |
| 500 | | 27–32 | 5 | 7–12 |
| 1250 | | 28–76 | 13 | 7–18 |

As reported previously (Phelps, 1946b (6)), the cyclic changes in the endometrial vascular bed (Daron, 1936 (3)) were produced in ovariectomized monkeys by injecting ovarian hormones in the manner illustrated in Fig. 1—the changes characteristic of the ovulatory cycle when both estrogen and progesterone were injected, those characteristic of the anovulatory cycle when only estrogen was injected. As observed in intraocular endometrial transplants, the estrogen phase of the experimental cycle produced by the administration of both hormones was characterized by progressive growth of arteries and capillary bed, the progesterone phase by marked arterial development, with increased coiling and tortuosity, formation of anastomoses and a sudden spurt of growth that brought the arteries to the endometrial surface at the stage of the experiment corresponding to the time of nidation. When only estrogen was administered, arterial growth

continued throughout the cycle but the marked vascular development and approximation of arteries and surface characteristic of the response to estrogen-progesterone did not occur.

The pattern of the vascular responses to estrogen-progesterone and estrogen, respectively, was constant. Certain quantitative aspects varied, e.g., extent of vascular growth, tortuosity of arteries, number of arteries activated and duration of bleeding. The variations in the duration of bleeding were noted not only in groups of experiments in which the hormone

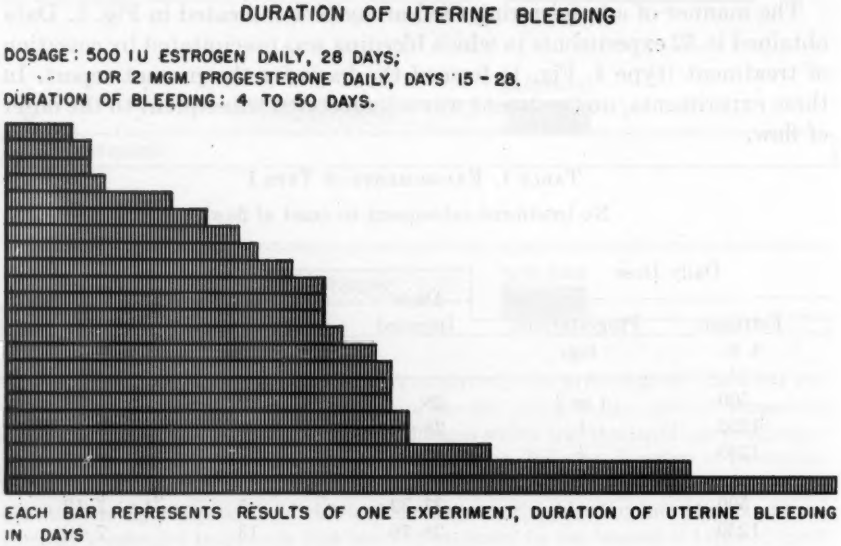
DURATION OF UTERINE BLEEDING
DOSAGE: 500 I U ESTROGEN DAILY, 28 DAYS;
1 OR 2 MGM. PROGESTERONE DAILY, DAYS 15 - 28.
DURATION OF BLEEDING: 4 TO 50 DAYS.
EACH BAR REPRESENTS RESULTS OF ONE EXPERIMENT, DURATION OF UTERINE BLEEDING IN DAYS

FIG. 2. Duration of the 22 episodes of uterine bleeding under discussion herein, without reference to treatment administered in previous experiments.

dosages employed were different but also in groups of experiments in which the dosages employed were the same (Table 1).

For example, a dosage of 500 international units (0.0166 mg.) of estrogen daily for 28 days, 1 or 2 mg. progesterone daily days 15-28 was administered in 22 experiments. The 22 episodes of uterine bleeding produced varied in duration from 4 to 50 days (Fig. 2.). No significant difference in the results obtained with 1 and 2 mg. of progesterone was apparent. The variations in the duration of bleeding could be correlated roughly with variations in the preexisting vascular structure and with variations in experimental treatment to which the animals had been subjected prior to administration of the dosage in question. By preexisting vascular structure is meant the

specific architecture of the vascular bed of the intraocular endometrial transplants at the beginning of any given course of injections.

An analysis of the 22 episodes of bleeding referred to above in relation to representative variables of the two types described is sufficient for present purposes. Analysis of the results obtained with each of the dosages employed in the study revealed correlations of similar import.

Results obtained in monkey #5 (Table 2) illustrate the relationships observed between the duration of bleeding and the preexisting vascular structure.

TABLE 2. RESULTS OBTAINED IN MONKEY #5; ALL EXPERIMENTS TYPE I

| Experiment | Daily Dose | | Duration of Injection Period, Days | Duration of Uterine Bleeding, Days* |
|---|---|---|---|---|
| | Estrogen, I. U. | Progesterone, mg. | | |
| 1 | 1250 | — | 41 | 8 |
| 2 | 500 | 2 | 28 | 22 |
| 3 | 1250 | ¼ | 43 | 7 |
| 4 | 500 | 2 | 28 | 41 |
| 5 | 500 | 2 | 28 | 29 |
| 6 | 500 | — | 28 | 8 |
| 7 | 500 | — | 28 | 12 |
| 8 | 500 | — | 28 | 7 |
| 9 | 500 | 2 | 28 | 12 |
| 10 | 1250 | — | 28 | 8 |
| 11 | 500 | 2 | 28 | 5 |
| 12 | 1250 | ¼ | 42 | 9 |
| 13 | 500 | 2 | 28 | 19 |

* Results obtained with the dosage discussed in the text are shown in the outer column.

At the end of experiment 1, the endometrial transplant in the left eye of this monkey was a thin, flat sheet of tissue hardly distinguishable from the iris. A few scattered vessels could be seen in it. It was attached to the iris near the pupil border in the 12 o'clock position and from this point extended upward toward the one o'clock position at the scleral margin.

Comparatively little growth took place in experiment 2. At the end of this experiment, the transplant still appeared as a thin, flat sheet of tissue with few vessels. However, it was a little larger in area than at the beginning of this experiment and extended downward across the upper part of the pupil.

Remarkable growth of the endometrial tissue and vascular bed took

place during experiment 3. At the height of its development in this experiment, the transplant covered about one-fourth of the iris. Two large arteries showed considerable growth during the estrogen phase and continued vascular development during the progesterone phase resulted in the production of an extensive superficial vascular network. Very little tissue was lost during the bleeding phase of the experiment. At the end of the bleeding phase, the transplant appeared as a fairly large and very well vascularized bulbous protrusion. From the under side of the bulbous portion, a thin, flat film extended downward covering most of the pupil. Thus the size of the transplant and the extent of its vascular bed were much greater at the beginning of experiment 4 than at the beginning of experiment 2. The duration of bleeding in experiment 4 was 41 days, as compared with 22 days in experiment 2.

The volume of the transplant at the end of experiment 4 was about the same as at the beginning of this experiment. At the end of experiment 5, the transplant was slightly smaller. It still had a well-developed vascular bed. However, the superficial network was somewhat less extensive and the pattern was different, as compared with conditions at the beginning of this experiment. In one circumscribed area, tissue formed as a result of the growth in experiment 3 became cystic in experiment 4 and was desquamated in experiment 5.

During experiments 6, 7 and 8, in which only estrogen was given, the superficial portion of the extensive vascular bed built up in experiment 3 and maintained in experiments 4 and 5 was destroyed, partly as a result of desquamation during the bleeding phases of these experiments and partly as a result of reversion of some of the arterial branches to a state of relative inactivity. The duration of the bleeding in experiment 9 was only 12 days.

During experiment 6, arterial twigs grew out from the margin of the iris below the bulbous portion of the transplant into the film covering the pupil. These new branches underwent some development during experiments 7 and 8 but at the end of each of these three experiments they became ischemic and, with the exception of a few tiny twigs, did not again become functional until the next course of treatment was started. During experiments 9 and 11 these branches underwent considerable development and bleeding took place from them.

Growth of the endometrial tissue and vascular bed during experiment 12 was greater than during experiment 10 but not as extensive as in experiment 3. The bleeding in experiment 13 was 19 days, as compared with 5 days in experiment 11 and 41 days in experiment 4.

The history of this monkey (#5) indicates that a single course of treatment with ovarian hormones may produce permanent as well as transitory

changes in the structure of the endometrial vascular bed. By transitory is meant changes that are lost during the period of regression and bleeding that follows cessation of treatment. By permanent is meant changes that are not lost during the period of regression. The permanent changes may represent an increase in the total extent of the vascular bed or they may represent a decrease. Extensive portions of the vascular bed built up in one cycle may be destroyed in subsequent cycles. The preexisting vascu-

TABLE 3. DURATION OF UTERINE BLEEDING IN RELATION TO TREATMENT ADMINISTERED IN PRECEDING EXPERIMENT

| Monkey | Preceding Experiment | | | Current Experiment* | |
|---|---|---|---|---|---|
| | Daily Dose | | Duration of Injection Period, Days | Number | Duration of Uterine Bleeding, Days |
| | Estrogen, I.U. | Progesterone, mg. | | | |
| 1 | 1250 | — | 76 | 5 | 6 |
| | 1250 | — | 50 | 12 | 5 |
| | 500 | — | 32 | 7 | 19 |
| | 500 | 1 | 28 | 8 | 23 |
| 2 | 1250 | — | 43 | 2 | 23 |
| | 25000 | 1 | 50 | 4 | 50 |
| | 500 | 2 | 28 | 5 | 24 |
| | 500 | 2 | 28 | 6 | 24 |
| 5 | 1250 | — | 41 | 2 | 22 |
| | 1250 | — | 28 | 11 | 5 |
| | 500 | — | 28 | 9 | 12 |
| | 1250 | ¼ | 43 | 4 | 41 |
| | 1250 | ¼ | 42 | 13 | 19 |
| | 500 | 2 | 28 | 5 | 29 |

* Dosage: 500 I.U. estrogen daily, 28 days, 1 or 2 mg. progesterone daily, days 15–28

lar structure may exert a profound influence upon the duration of any single epsiode of bleeding.

Comparison of the duration of bleeding in experiments 2 and 4 and 11 and 13 indicates that the stimulus acting in the preceding cycle has an important influence upon the duration of the bleeding in the current cycle. Comparison of the results of experiments 1–4 with those of experiments 10–13 indicates that the stimulus acting during the immediately preceding cycle is not the only factor in the previous history that influences the current bleeding. An influence of several previous cycles of stimulation may be evident.

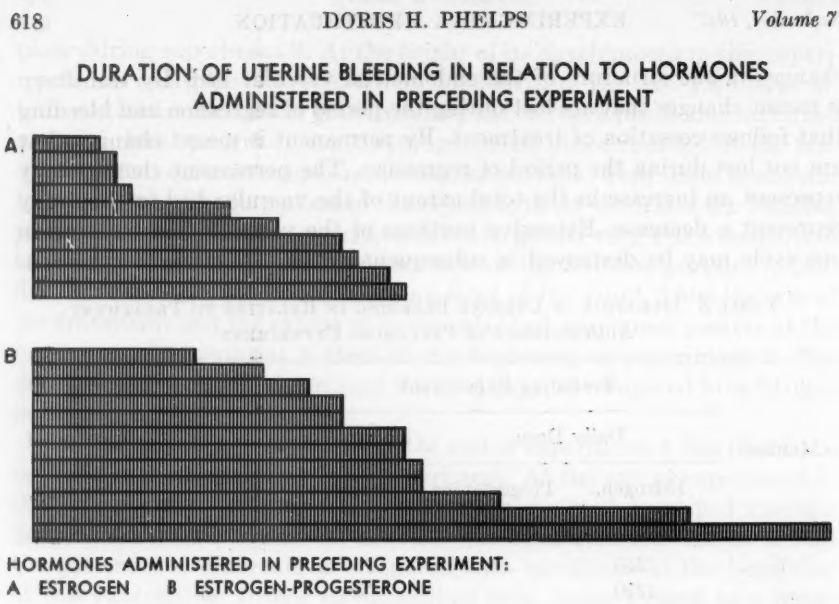
DURATION OF UTERINE BLEEDING IN RELATION TO HORMONES ADMINISTERED IN PRECEDING EXPERIMENT
A.
B
HORMONES ADMINISTERED IN PRECEDING EXPERIMENT:
A ESTROGEN B ESTROGEN-PROGESTERONE

FIG. 3. Duration of uterine bleeding in relation to hormones administered in the preceding experiment. The bars represent the 22 episodes of bleeding under discussion herein. Each bar indicates the duration of one episode in days. A. Estrogen administered in preceding experiment, duration of 'current' bleeding 4–23 days. B. Estrogen-progesterone administered in preceding experiment, duration of 'current' bleeding 10–50 days.

TABLE 4. DURATION OF UTERINE BLEEDING IN CURRENT EXPERIMENT IN RELATION TO HORMONES ADMINISTERED IN PRECEDING EXPERIMENT

| Preceding Experiment | | Current Experiment | | |
|---|---|---|---|---|
| Hormones Administered | Duration of Injection Period, Days | No. of Experiments | Duration of Uterine Bleeding, Days Range | Average |
| Estrogen | 27–32 | 4 | 5–20 | 14.0 |
| Estrogen-Progesterone | 28 | 6 | 10–29 | 22.1 |
| Estrogen | 41–43 | 3 | 15–23 | 20.0 |
| Estrogen-Progesterone | 42–46 | 4 | 14–41 | 22.5 |
| Estrogen | 50–76 | 3 | 4–6 | 5.0 |
| Estrogen-Progesterone | 50, 148 | 2 | 50, 19 | 34.5 |
| Estrogen | 27–76 | 10 | 4–23 | 13.1 |
| Estrogen-Progesterone | 28–148 | 12 | 10–50 | 24.4 |

The correlations observed between the duration of bleeding and variations in the treatment administered in the experiment immediately preceding afford evidence concerning which aspects of previous treatment may influence the duration of the current[2] bleeding.

The results obtained in monkeys #5, #1 and #2 (Table 3) are particularly significant, since these animals each received 4 or more courses of treatment with the dosage under discussion. In the case of monkey #5 a relation-

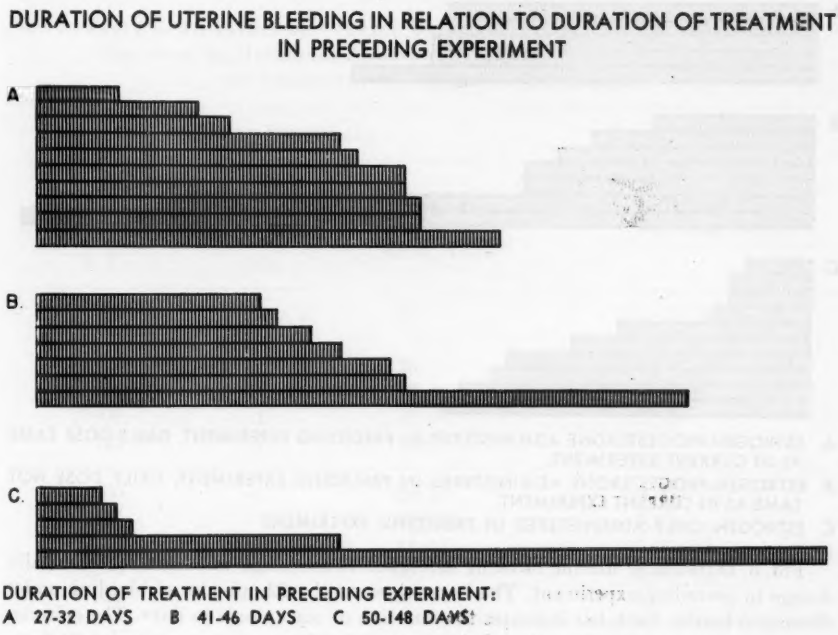
DURATION OF UTERINE BLEEDING IN RELATION TO DURATION OF TREATMENT IN PRECEDING EXPERIMENT
A
B
C
DURATION OF TREATMENT IN PRECEDING EXPERIMENT:
A 27-32 DAYS B 41-46 DAYS C 50-148 DAYS

FIG. 4. Duration of uterine bleeding in relation to duration of the preceding experiment. The bars represent the 22 episodes of bleeding under discussion herein. Each bar indicates the duration of one episode in days. A. Duration of preceding experiment 27–32 days, duration of 'current' bleeding 5–29 days. B. Duration of preceding experiment 41–46 days, duration of 'current' bleeding 14–41 days. C. Duration of preceding experiment 50–148 days, duration of 'current' bleeding 4–50 days.

ship between the duration of the current bleeding and the hormones administered in the preceding experiment was apparent, in monkey #1, between the duration of the current bleeding and the duration of the pre-

[2] In the discussion to follow, the word 'current' is used to designate the experiments in which the dosage under discussion was administered.

ceding experiment. Certain variations in the duration of episodes produced in monkeys #2 and #5 could be correlated with variations in the estrogen-progesterone balance in the preceding experiment.

The correlations observed in the group as a whole between the duration of the current bleeding and the hormones administered in the preceding

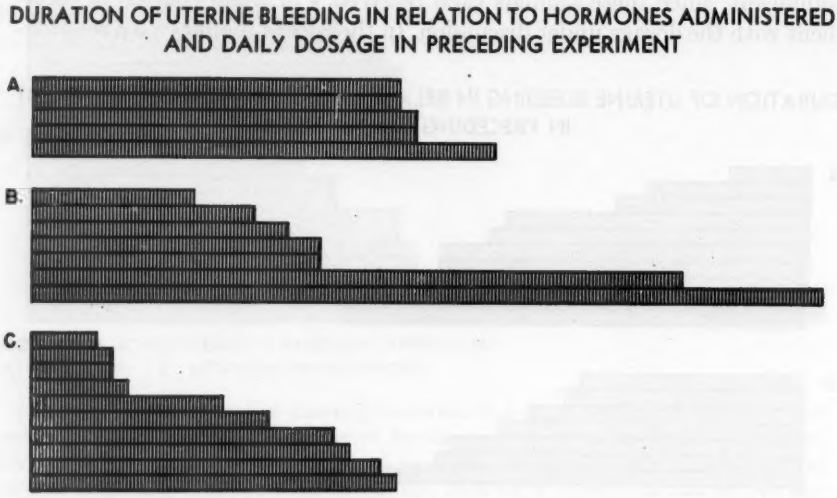
DURATION OF UTERINE BLEEDING IN RELATION TO HORMONES ADMINISTERED AND DAILY DOSAGE IN PRECEDING EXPERIMENT
A.
B.
C.
A ESTROGEN-PROGESTERONE ADMINISTERED IN PRECEDING EXPERIMENT, DAILY DOSE SAME AS IN CURRENT EXPERIMENT.
B ESTROGEN-PROGESTERONE ADMINISTERED IN PRECEDING EXPERIMENT, DAILY DOSE NOT SAME AS IN CURRENT EXPERIMENT.
C ESTROGEN ONLY ADMINISTERED IN PRECEDING EXPERIMENT

FIG. 5. Duration of uterine bleeding in relation to hormones administered and daily dosage in preceding experiment. The bars represent the 22 episodes of bleeding under discussion herein. Each bar indicates the duration of one episode in days. The episodes in question were produced by the administration of 500 I.U. estrogen daily for 28 days, 1 or 2 mg. progesterone daily days 15–28 ('current' experiment). A. Estrogen-progesterone administered in preceding experiment, dosage same as in 'current' experiment; duration of 'current' bleeding 23–29 days. B. Estrogen-progesterone administered in preceding experiment, dosage not same as in 'current' experiment, duration of 'current' bleeding 10–50 days. C. Estrogen administered in preceding experiment, duration of 'current' bleeding 4–23 days.

experiment are shown in Fig. 3. Comparison of the results obtained subsequent to estrogen and estrogen-progesterone administration, respectively, revealed a tendency toward greater prolongation of bleeding in those instances in which both hormones were administered in the preceding experiment. This tendency was still apparent when the factor of variation in the duration of the preceding experiment was eliminated (Table 4).

Fig. 4 shows the duration of the current bleeding in relation to the duration of the preceding experiment. Of interest are 1) the consistent prolongation of bleeding following experiments of 41–46 days' duration (Fig. 4, group B) and 2) the wide range of variation subsequent to prolonged treatment (Fig. 4, group C). An influence of the duration of the preceding experiment was still evident when the factor of variation in the hormones administered was eliminated (cf. Table 5).

The correlations between the duration of the current bleeding and variations in the dosages administered in the current and preceding experiments are shown in Fig. 5 and Table 5. Of particular interest are 1) the consistency of the results obtained in the instances in which the hormones administered, daily dosage and duration of treatment were the same in the current and preceding experiments (group A, Fig. 5), 2) the variation in the instances in which one or more of these factors was not the same in the two experiments (groups B and C, Fig. 5) and 3) the range of variation in each of the groups in Fig. 5 as compared with the range in the other two groups.

TABLE 5. DURATION OF UTERINE BLEEDING IN CURRENT EXPERIMENT IN RELATION TO HORMONES ADMINISTERED, DAILY DOSE AND DURATION OF TREATMENT IN PRECEDING EXPERIMENT

| Preceding Experiment | | | Current Experiment* |
|---|---|---|---|
| Daily Dose | | Duration of Injection Period, Days | Duration of Uterine Bleeding, Days |
| Estrogen, I. U. | Progesterone, mg. | | |
| 500 | 1 or 2 | 28 | 23, 23, 24, 24, 29 |
| 1250 | 1 | 28 | 10 |
| 1250 | ¼ | 42–44 | 14, 19, 41 |
| 25000 | 1 | 46, 50 | 17, 50 |
| 125 | ¼ | 148 | 19 |
| 500 | — | 28, 32 | 12, 19 |
| 1250 | — | 27, 28 | 5, 20 |
| 1250 | — | 41–43 | 15, 22, 23 |
| 1250 | — | 50, 76 | 5, 6 |
| 125 | — | 51 | 4 |

* Dosage: 500 I.U. estrogen daily, 28 days, 1 or 2 mg. progesterone days 15–28.

It seems evident from the data presented in Fig. 3–5 and Table 5 that

uterine bleeding is influenced by each of the following factors: 1) components of the hormonal stimuli acting in previous cycles, 2) duration of previous cycles of stimulation and 3) qualitative and quantitative variation in the stimuli acting in successive cycles. Further study is required to determine the specific influence of each of these factors and the significance of their interaction.

In a previous report (Phelps, 1946a (5)) evidence was presented which indicates that the duration of uterine bleeding is influenced by the components and relative strength of the current hormonal stimulus. The results described herein afford evidence that any given episode of uterine bleeding is also influenced by the components, relative strength and duration of action of hormonal stimuli acting prior to application of the current stimulus. In other words, the influence of a single course of stimulation by ovarian hormones is not limited to the cycle which that course of stimulation represents. Its influence extends through at least one subsequent cycle and probably through more than one. This influence upon subsequent cycles is mediated at least in part through the structural changes produced in the endometrial vascular bed. These changes may be transient or permanent, i.e., carried over into the next cycle. The specific vascular architecture existing at the beginning of any single cycle has an important influence upon the duration of the uterine bleeding in that cycle.

From the practical standpoint, the significance of these findings lies chiefly in the implication that the 'preexisting vascular structure' is one of the factors concerned in the control of uterine bleeding and the demonstration that this factor is subject to alteration as a result of previous hormonal stimulation. Ovarian failure is characterized by variation from time to time in qualitative and quantitative aspects of the endocrine activity of the ovaries. It seems reasonable to assume, therefore, that the preexisting vascular structure, i.e., the structure of the endometrial vascular bed at the beginning of the growth phase of the cycle, is not constant in ovarian failure. In any case, this factor should be taken into consideration in evaluating menstrual symptoms, results of therapy and any other clinical or experimental evidence concerning the action of specific hormones or hormone dosages upon the endometrium.

## SUMMARY

To obtain information concerning local vascular mechanisms involved in the production of menstrual abnormalities, nine ovariectomized rhesus monkeys were injected with various combinations of the ovarian hormones. Endometrial vascular phenomena were observed by means of intraocular endometrial transplants and these observations were correlated with observations on uterine bleeding. One hundred seven episodes of uterine

bleeding were produced. Analysis of the results of single experiments in relation to treatment administered in previous experiments in the same animal revealed that 1) the influence upon the endometrium of a single course of treatment with ovarian hormones may extend through one or more subsequent cycles, 2) permanent changes in the structure of the endometrial vascular bed may result from stimulation by the ovarian hormones, 3) the architecture of the endometrial vascular bed at the beginning of any given course of treatment with ovarian hormones influences the duration of the uterine bleeding produced by that course of treatment.

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# THE CLINICAL SIGNIFICANCE OF HYPEROSTOSIS FRONTALIS INTERNA

NORMAN G. SCHNEEBERG, GEORGE WOOLHANDLER AND RACHMIEL LEVINE

*From the Department of Metabolism and Endocrinology, Research Institute, and the X-Ray Department, Michael Reese Hospital, Chicago*

IN THE 182 years since Morgagni and Santorini (23) first described obesity and virilism associated with the thickening of the internal table of the frontal bone called *Hyperostosis Frontalis Interna* (HFI) a voluminous literature has accumulated dealing with this peculiar osteopathy. With few exceptions (11, 14, 32) great clinical importance has been attached to its presence and the concept that it constitutes a distinct entity has been held by most authors. That the syndrome represents evidence of either endocrine or metabolic pathology has received such universal accord that the diagnosis of *Metabolic Craniopathy* (19, 12) has been incorporated in the recent literature.

The evidence of the existence and distinctiveness of the HFI syndrome has depended largely upon a description of isolated cases or of groups of cases presenting the signs and symptoms considered characteristic of HFI. There has been no attempt in the reported work to compare the clinical features of cases of HFI with the clinical features of a control series of patients without HFI. Because doubt has been expressed in the literature as to the existence of HFI as a clinical entity (14, 32) such a study would be fundamental to a clarification of the subject. We are, therefore, reporting the results of such a comparison of cases of HFI with a control group of patients without HFI; in addition we have reviewed the literature and analyzed our own cases with the purpose of studying the specificity of the HFI syndrome.

The term *Hyperostosis Frontalis Interna* (HFI)[1] refers to a non-inflammatory, frequently symmetrical thickening of the internal table of the frontal bone of the skull. This hyperostosis may or may not extend to adjacent bony areas or to the falx cerebri but it does not involve the external skull surface and thus does not increase the external skull dimensions. Examples of the easily recognized bony thickenings in skull x-rays are shown in Fig. 1. The radiological characteristics have been completely described in Moore's several papers (19, 20, 21).

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[1] Synonyms: Morgagni's syndrome, Stewart-Morel syndrome, Metabolic Craniopathy, Calvarial Hyperostosis, Enostosis of the Calvarium, Exostoses within the Cranium, Intracranial Osteophytes.

The diagnosis depends upon the discovery of HFI associated with any of the following clinical features;—obesity, psychoneurosis and/or psychosis, headache, hirsutism, mental retardation or deterioration, weakness, vertigo, menstrual disorders, tinnitus, hypertension, neurologic disorders, visual disturbances, convulsions, somnolence, lethargy, fatigue, epilepsy,

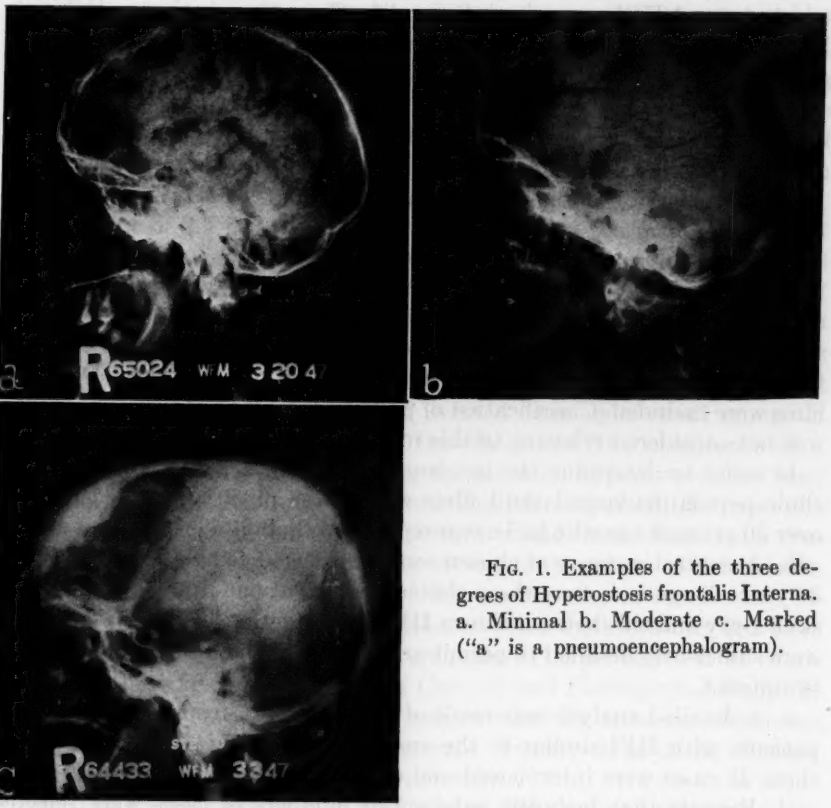


FIG. 1. Examples of the three degrees of Hyperostosis frontalis Interna. a. Minimal b. Moderate c. Marked ("a" is a pneumoencephalogram).

narcolepsy, diabetes mellitus and diabetes insipidus. The first four enumerated might be considered the cardinal features for these are the most commonly reported in the literature.

In 1765 Morgagni and Santorini described the postmortem findings of an obese masculinized 75 year old female who showed numerous intracranial osteophytes of the frontal bone and several bony nodules on the petrous bones. Little clinical significance was ascribed to these changes. In 1928 Grieg (11) recorded his extensive autopsy experiences and exami-

nations of the skulls in the Museum of the Royal College of Surgeons of Edinburgh. He concluded that intracranial osteophytes were very common in old women and were not associated with any particular clinical picture. Most of the literature on the subject, however, stems from Stewart's description (31) in 1928, of 5 insane obese females exhibiting HFI at post-mortem and from Morel's report (22) of a case of obesity, mental disturbances and HFI recognized during life. Since then patients exhibiting HFI with obesity and virilism have been called representative of the Morgagni syndrome; when obesity, mental disturbances and HFI co-exist, the eponym Stewart-Morel syndrome has been used. Knies and LeFever (16), in an exhaustive review of the literature, collected reports of some 300 autopsy and museum specimens and 175 clinical cases from 1900 to 1941.

## METHODS

The data to be presented have been acquired in the following manner:

a. In order to determine the incidence of HFI in patients who had once required a skull x-ray as part of their case study 150 successive unselected skull films taken in the Mandel Clinic were reviewed. A positive film had to show unequivocal hyperostosis to more than one observer. Doubtful films were excluded. Classification of positive cases into Moore's subgroups was not considered relevant to this investigation.

In order to determine the incidence of HFI in a general hospital and clinic population lateral skull films were taken of 50 unselected females over 30 years of age who had never required a skull film prior to this study.

b. A control group was chosen consisting of 50 female clinic patients, 30 years of age and over, whose clinical picture at one time had required a skull x-ray and this had not shown HFI. Cases were selected whose records were sufficiently detailed to permit an analysis of the significant signs and symptoms.

c. A detailed analysis was made of the clinic and hospital records of 25 patients with HFI similar to the analysis of the control group. Most of these 25 cases were interviewed and examined by the authors.[2]

d. Reports that included substantial numbers of cases were selected from the literature for analysis. Single case reports have not been included. A total of 657 cases was collected. There was no attempt to review the literature completely.

Certain of our criteria in evaluating the importance of signs and symptoms must be elucidated. Cases were classified as showing minimal, moderate or marked HFI on the basis of the degree of the thickening of the

[2] Doctors Taubenhaus, Bucy (Chicago Memorial Hospital), Allweiss, Sideman, Horner, Spiegel and Boshes permitted us to include their cases.

frontal bone. A representative case of each type is shown in Fig. 1. A patient was considered obese if she was 20 per cent or more above maximum ideal weight (Metropolitan Life Insurance Tables) or if the statement that the patient was obese was repeated several times in the record. "Hirsutism" referred to facial hypertrichosis that was readily evident at a glance and which required removal for cosmetic reasons. A patient was classified as "psychoneurotic" when an important part of his clinical picture was psychogenic in origin. "Hypertension" required a persistent elevation of the diastolic blood pressure to 90 or above.

**Incidence.** The incidence of HFI reported by several authors varies from 0.014 per cent (20) to 40 per cent (14) with an average of approximately 7 per cent. We discovered 4 cases among 150 successive skull films of clinic patients whose clinical status required skull radiograms for various reasons, an incidence of 2.7 per cent. In order to determine the incidence of HFI in a group of women over 30 years of age constituting a general hospital and clinic population, 50 successive women were x-rayed and 6 cases of HFI were discovered, an incidence of 12 per cent.

It is evident that HFI cannot be considered a rare skull anomaly; yet the occurrence of the HFI syndrome has been considered of sufficient moment to warrant the reporting of isolated cases or of small groups of cases in the literature. It appears, therefore, that the occurrence of a specific clinical picture accompanying the calvarial hyperostoses has been merely a fortuitous relationship where it has been reported; the cases not representing the so-called typical picture would have been more frequently revealed in any survey study of sizeable numbers of individuals.

**Sex.** The striking predominance of this craniopathy in females has intrigued all observers. Of 657 cases collected from the literature, 582 were females (88.6 per cent) and only 75 were males (11.4 per cent). If we eliminate from these figures the reports of Carr (6) and Eldridge and Holm (9) who confined their studies to females only, we find the incidence of females to be 84.4 per cent and males 14.6 per cent. Twenty-three of the 25 cases of HFI we studied were females (92 per cent).

**Age.** The greatest incidence of HFI is in middle-aged and elderly females though cases have been reported in teen-age children (16). The average age of cases collected from the literature was 46 years. Among our 25 patients there was an almost even distribution from the third to the seventh decade. The average age was 47.6 years with 11 cases younger than the median and 14 cases older than the median age. The degree of hyperostosis bore no relationship to age, our 6 most severe cases being 27, 31, 35, 49, 55 and 65 years old. Critchley (7) stated that a uniform increase in calvarial thickening occurs in old age which at times forms focal osteophytic processes. He considered HFI a somewhat rare example of these osteophytes.

**Clinical Features.** Eleven papers (23, 11, 14, 32, 19–20–21, 12, 16, 9, 6, 5, 28) were selected from the literature which presented enough detailed data to permit a tabulation of the clinical features considered significant in the HFI syndrome. The incidence of important clinical features in the total of 657 cases from these sources is compared with the 25 cases we observed and with the control group of 50 females without HFI (Table 1). The average ages for the three groups is 46, 47.2 and 47 years. It is evident that there is no significant difference between them. Of the four cardinal

TABLE 1. A COMPARISON OF THE CLINICAL FEATURES OF 657 CASES OF HFI GATHERED FROM THE LITERATURE AND 25 CASES FROM MICHAEL REESE HOSPITAL (MRH) WITH A CONTROL GROUP OF FEMALE CLINIC PATIENTS OVER 30 YEARS OF AGE WITHOUT HFI

| | Literature | MRH | Control |
|---|---|---|---|
| Females | 89% | 92% | 100% |
| Average age | 46 | 47.2 | 47 |
| Obesity (I) | 31% | 56% | 70% |
| Hirsutism (II) | 27 | 22 | 10 |
| Headache (III) | 29 | 48 | 54 |
| Psychoneurosis (IV) | 67 | 44 | 64 |
| Mental Deterioration or Retardation | 35 | 8 | 2 |
| Neurologic Disorders | 17 | 8 | 18 |
| Hypertension | 21 | 40 | 40 |
| Menstrual Disorders | 23 | 16 | 40 |
| Tinnitus | 21 | 4 | — |
| Visual Disturbances | 15 | 24 | 10 |
| Vertigo | 25 | 36 | 34 |
| Convulsions and Epilepsy | 11 | 4 | 2 |
| Somnolence | — | 4 | 6 |
| Lethargy | — | 0 | 10 |
| Muscular Weakness | 27 | 44 | 34 |
| Fatigue | — | 56 | 36 |
| Diabetes Mellitus | 4 | 16 | 22 |

features (I, II, III and IV in Table 1) obesity is strikingly more frequent among the controls than in HFI, headache is more frequent in the control group, psychoneurosis is as frequent, and only hirsutism shows a definitely greater incidence among the positive cases. If we add the incidence of the 17 features listed in Table 1 we find in a total of 7 of these features the control group showed the greatest percentage, in 5, the cases collected from the literature predominated, and in 4, our own group of HFI cases presented the greatest frequency of clinical features.

This comparison does not lend itself to a careful statistical evaluation and is open to criticism for several reasons. The groups differ greatly in

total numbers. The evaluations of the 657 cases from the literature were made from eleven different sources with the inevitable differences in criteria, judgment and methods of selection. If we confine our attention, however, to the smaller groups observed in our clinic, the comparison yields the same conclusion. Here again, of the four cardinal features, only hirsutism occurred more often among the HFI cases than among the controls and the incidence of total features occurring with the greater frequency is divided evenly (8 and 8) between the two groups.

Seven of our 25 cases exhibited HFI, obesity and psychoneurosis and would be diagnosed as Stewart-Morel syndrome. We have not encountered an instance of the so-called Morgagni syndrome which comprises HFI with obesity and virilism though 4 of our patients showed HFI, obesity and hirsutism. Two cases exhibited all four of the cardinal features but in 4 cases none of the four existed. Of 6 cases showing only one cardinal feature accompanying HFI, 3 complained of headaches alone, 2 were only obese and 1 was a psychoneurotic. A similar analysis of the control group showed 5 cases with obesity and hirsutism and 22 cases with obesity and psychoneurosis. One control case exhibited the four cardinal features.

The conclusion based on these comparisons becomes inevitable, namely, that the clinical features considered pathognomic of the HFI syndrome can be found as often or oftener among cases without HFI as in those presenting the classical skull changes.

If HFI bears any relationship to the various signs and symptoms to which it has been linked some degree of parallelism should be evident between the severity of the clinical features and the degree of the hyperostosis. Furthermore, progression of the various features should frequently be associated with an increase in the bony thickening. With a single exception (20) neither observation has been made by proponents of the specificity of the syndrome. We classified our cases of HFI as minimal, moderate or marked based on the amount of calvarial thickening and similarly tabulated each clinical feature based on its severity. No relationship between the severity of the hyperostoses and the clinical features was found.

If a syndrome characteristic of HFI exists it should be unusual to find a similar clinical picture occurring in patients without calvarial hyperostoses. In a relatively short time we have observed several such cases and 3 representatives are briefly summarized:

1) Mandel Clinic *No. 39036B.* A 37 year old white female. Complaints: vague abdominal pain, intermittent amenorrhea since 1934; 30 lb. weight gain in 3 years; occipital headaches, nocturia, "sticking pains" in arms for one year. 1938-Resection of ovarian cyst. 1939-Diabetes mellitus. Phys. Exam: Mentally retarded, moderately obese. B. P. 138/78. Facial hirsutism requiring shaving every other day, abdominal linea striae, left

ovarian cyst. Comment: This case exhibits obesity, hirsutism, headaches, mental retardation, menstrual disorder, diabetes mellitus. The skull x-ray was negative.

2) Mandel Clinic *No. 47197B.* A 48 year old white female. Complaints: referred to every body system with emphasis on severe headaches, marked fatigue, weakness: previous menorrhagia required hysterectomy. 1940: Diabetes mellitus. Psychiatric opinion: "deepseated masochistic character disturbance with superimposed conversion symptoms." Phys. exam: Marked obesity, extreme nervousness, B.P. 134/80. No hirsutism. Comment: Psychoneurotic patient with headaches, obesity and diabetes mellitus. Skull x-ray was negative.

3) Mandel Clinic *No. 89224.* A 51 year old white female observed since 1932. Complaints: multitudinous, referred to all body systems but primarily gastro-intestinal and cardiac. Severe headaches, marked weight gain, hot flashes, tinnitus. Phys. exam: Extremely obese, mild hirsutism (plucks facial hair), BP 110/80, varicose veins. Studies: Hypertrophic arthritis of spine, sacro-iliac arthritis, anemia. 1940: Diabetes mellitus. Comment: Psychoneurotic patient with extreme obesity, mild hirsutism, headaches, diabetes mellitus. Skull x-ray was negative.

**Asymptomatic Cases.** Few symptomless cases of HFI have been reported, probably because skull x-rays are usually obtained only in patients presenting complaints referable to the head or indicative of an endocrinopathy and because skull x-ray surveys to determine the incidence of HFI in the general population have rarely been done. When we carried out such a survey study of 50 women 1 symptomless case of HFI was discovered. Grollman and Rousseau (12), who carried out a similar survey, found 2 cases where they considered the skull changes to be merely an incidental finding. Knies and Le Fever (16) discovered HFI in 5 asymptomatic children aged 13 to 19 though 3 of them who were siblings were mentally retarded. The argument has been advanced (12) that symptomless cases will eventually develop the clinical picture of the HFI syndrome because of the progressive nature of the disease. Moore's statement that "in all probability the symptoms antedate the osseous changes" would tend to refute this view. Evidence for progression of the bony changes is scanty (21, 16, 26, 17, 29, 28) with only Eisen and Lehoczky and Orban reporting x-ray studies to confirm this impression. Since most authorities believe that the clinical symptoms and hyperostoses do not parallel each other in severity there is no evidence that the symptomless case, given time, will develop the fullblown HFI syndrome.

**Neuropsychiatric and Mental Disturbances.** The association of psychoneurosis, psychosis, mental retardation and neurologic disturbances with cranial hyperostoses has appeared striking. Studies like those of Eldridge and Holm (9), who found HFI in 50 of 200 successive patients admitted to a mental institution, appear to indicate some distinct relationship between the bony thickenings and the central nervous system. The possibility that the hyperostoses might be responsible for mental aberrations by direct pressure on the frontal lobe of the brain is an attractive hypothesis. Psy-

chiatric patients represent a group most intensively studied for the presence of cranial hyperostoses probably because of the impetus derived from the early reports of Stewart and Morel. In addition skull x-rays are done in many such cases as part of their routine study and for this reason alone many cases have been uncovered. The 25 per cent incidence reported by Eldridge and Holm (9) loses its significance when we find Henschen (14), whose writings indicate an extensive autopsy experience in searching for cranial enostoses, reporting HFI in about 40 per cent of all autopsied females over 40 years of age. As for the possibility of direct cerebral damage caused by the hyperostoses, the evidence militates against such an occurrence. First, because no uniform psychiatric or neurologic picture is associated with HFI (9). Second, because in most instances, signs and symptoms of a neurologic disorder could not be localized to the cerebral region adjacent to the hyperostoses (6, 28). Third, because psychoneurosis and neurologic disorders were found as frequently in the control series of cases without hyperostosis as in patients showing typical frontal bone thickenings and nodulations.

Canavan (5) did find brain atrophy in the frontal region where enostoses occurred in 74 cases but stated that such atrophy was a common change in mental disease. Hemphill and Stengel (13) felt that the progressive dementia and neurologic signs in their *case 1* could be explained by brain encroachment but added that the frontal and parietal lobes are most heavily involved in any of the chronic degenerative changes of the cortex and the concept that direct action of the bony condition on brain function is the cause of neurologic or psychiatric changes was not acceptable. Frontal cortical atrophy with HFI has been reported by others (10, 18, 26) but the general opinion appears to be that the atrophy and the hyperostosis are independent manifestations of a generalized process (3).

**Endocrine Nature of HFI.** Reifenstein's recent observation (27) that "obscure diseases usually are not made lucid by incriminating the endocrines," applies to the study of HFI. Here again Stewart's report, which included a description of pituitary changes in 3 of his 5 cases, provided the stimulus for a search for an endocrinopathy and especially for pituitary pathology in cases of HFI. Though the relationship of obesity to anterior pituitary disease has been disproven by the classical investigations of Camus and Roussy (4), Bailey and Bremer (1), P. E. Smith (30) and Hetherington (15), the concept still is popular and is marshalled as evidence for the endocrine etiology of the HFI syndrome. The production of cranial sclerosis in rats by the injection of "purified growth hormone" and "crude pituitary extracts" by Mortimer (24) is frequently quoted as evidence for the pituitary etiology of HFI. Mortimer did not claim to produce cranial hyperostoses, a fact which has not been mentioned in connection with his investigations.

We have observed HFI associated with hyperparathyroidism, hyperthyroidism, acromegaly and the adrenogenital syndrome and the literature contains reports of HFI with myxedema, acromegaly and Cushing's disease. This association of HFI with clearcut endocrinopathies might conceivably be considered evidence for an etiological relationship. The great majority of patients with HFI show no signs of endocrine disease, however, and the very dissimilarity of the diseases listed should dispel ideas of any direct connection. The frequency of hirsutism might indicate some endocrine cause. The etiology of hirsutism remains obscure. Bissell and Williams (2) concluded, from a thorough study of the subject, that the majority of hirsute women showed no demonstrable endocrine disease. They reported that the skull x-rays of their 33 carefully studied patients were negative.

The almost exclusive predilection of any disease for one sex always suggests some sex-linked hormonal cause for the observed anomaly. Yet in the various conditions in which this obtains, such as gout, Buerger's disease and alopecia of the male, no endocrine cause has been established and the predilection of HFI for the female remains unexplained.

**Metabolic Nature of HFI.** The diagnostic designation "metabolic craniopathy" has been suggested in lieu of HFI as a more suitable term because of the generalized nature of the disease. The alleged frequency of obesity where HFI is found and the concept that obesity is a metabolic disorder are the principal reasons for the substitution of this vague diagnostic eponym. That obesity is not a metabolic disorder but simply the result of storage as fat of an excess of caloric intake over need has been amply confirmed by many investigators (25).

The probability of a disturbance in calcium metabolism has been accepted by some (6, 20) as the cause of HFI. The localization of the lesions in the skull with absence of other bony pathology and the normal serum calcium and phosphorus studies found in 46 cases (32, 12) should dispel such a concept. Careful studies of calcium balance, however, have not been reported.

Basal metabolic rate and cholesterol determinations, where performed, have revealed no significant abnormalities.

It appears evident that the term "metabolic craniopathy" contributes little to a clearer understanding of the nature of HFI.

**The Hypothalamus and HFI.** With greater appreciation of the vital importance of the hypothalamus in recent years the tendency to link it to various obscure diseases of unknown etiology is to be expected. The autopsy findings of hypothalamic changes in several cases of HFI has suggested an etiological relationship. Reports of cellular changes in the supraoptic nuclei (13), lesions in the floor of the third ventricle (22), and a

questionable solid tumour of the hypothalamic region (20), as well as rare instances of diabetes insipidus (11), are presented in evidence. At the present time the only clinical features that clearly are of hypothalamic origin are diabetes insipidus, temperature and sleep regulation disturbances, experimental obesity in animals, Frohlich's syndrome and experimental manic and rage-like syndromes. In addition, it appears probable that impulses, originating in or transmitted by the hypothalamus, influence the anterior pituitary in causing precocious puberty, ovulation in rabbits, thyroid hypertrophy in response to cold, the alarm reaction (Selye) and possibly hyperthyroidism. It is also known that the hypothalamus has important connections with various cerebral centers. We cannot, in our present state of knowledge, implicate the hypothalamus as the cause of HFI or of most of the protean manifestations that may accompany it.

The numerous theories of the cause of HFI have been amply discussed in the many papers on the subject and since they contribute little to our understanding of this cranial osteopathy, a discussion of them would not be germane to the purpose of this report.

## COMMENT

This survey of the subject has led us to conclude that no real clinical entity characteristic of HFI exists. The bony thickenings of the internal table of the frontal bone represent a not uncommon incidental finding discovered either by x-ray of the skull or at postmortem and are unrelated to the clinical status of the patient. This conclusion has been based on the evidence presented which is summarized as follows: (1) Though HFI is not a rare finding when skull x-rays of women are carried out, the distinctive clinical picture supposedly linked to it is rare. (2) The clinical features considered pathognomic of the HFI syndrome were found as frequently and sometimes with greater frequency in a control series of women without HFI. (3) There was no parallelism evident between the severity of the clinical features and the degree of the hyperostosis. (4) Many cases have been discovered presenting what are considered the typical features of the HFI syndrome but without the calvarial changes. (5) Symptomless cases with HFI occur. (6) The concept that HFI is closely linked to various psychiatric and neurologic disorders is not valid from the evidence available. (7) There is no evidence to indicate that endocrine, metabolic or hypothalamic pathology causes HFI. (8) The clinical features found in cases of HFI have been so varied that no semblance of unity can be found. A great variety of unrelated disease processes may accompany HFI and can bear no definite relationship to the skull changes.

Our experience with one patient has suggested that the artificial group-

ing of dissimilar clinical features into an entity may elicit certain undesirable sequelae. The various complaints and physical signs displayed by this particular patient had all been ascribed to the presence of a minimal HFI and she had been led to believe that she suffered from an incurable malady. Possibly because of this her psychoneurotic manifestations became deep-rooted and her marked obesity and headaches could not be treated.

## SUMMARY

The question of the existence of a distinct clinical entity accompanying hyperostosis frontalis interna has been investigated. Six hundred and seventy-five cases from the literature and twenty-five of our cases have been analyzed and their clinical features compared to a control series of patients without HFI. The analysis indicates that HFI is a not uncommon incidental skull thickening in women that is unrelated to whatever clinical state may accompany it.

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# ACROMEGALY ASSOCIATED WITH AMYOTROPHIC LATERAL SCLEROSIS AND ACROMEGALY OF THE AMYOTROPHIC TYPE

## REPORT OF 3 CASES

E. PERRY McCULLAGH AND J. S. HEWLETT

*Cleveland Clinic, Cleveland, Ohio*

IT IS always intriguing to study the association of two diseases in which the cause of one is obscure. Under such circumstances ailments previously considered as separate entities have since been found to constitute a single disorder, thereby suggesting the cause and sometimes the cure for the disease. For example, the discovery of pituitary tumor led the way to our knowledge of the source of acromegaly and the development of much information concerning the endocrine control of growth. Generalized osteitis fibrosa cystica was described before it was known that the disease was associated with parathyroid tumors and, through the discovery of their association, hyperparathyroidism was eventually understood.

It is obvious that no causal relationship between acromegaly and amyotrophic lateral sclerosis or muscular dystrophy has been discovered. Nevertheless, we believe that the coexistence of the apparently related changes in the 3 patients reported here as well as similar instances from the literature may represent more than mere coincidence. It may be that the peculiar metabolic imbalance which existed has had a more direct bearing upon the results than can be readily attributed to the disease as we know it. All 3 of our patients suffered from frank acromegaly, and the diagnosis of amyotrophic lateral sclerosis was made in each one by the consultant in neurology. One of the patients died, and the diagnosis of amyotrophic lateral sclerosis was proved at autopsy. We recognized that the subsequent improvement manifested by the remaining 2 patients rendered the diagnosis of amyotrophic lateral sclerosis, as usually accepted, less certain in them, and for that reason these cases might be better classified as the amyotrophic type of acromegaly.

Several similar examples are to be found in the literature. As early as 1891 Duchesnau described the "amyotrophic form of acromegaly," in which he found degeneration of the root fibres in the posterior columns (5). In 1894 Tamburini (11) found in acromegaly a slight degeneration of the root zone in Burdach's column in the cervical and dorsal regions. Schultze (10) described the posterior columns of the cervical region in a patient with

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acromegaly as being somewhat lighter with rarefied nerve fibres. Dallemagne (4) presented a patient who had acromegaly and severe central nervous system arteriosclerosis with degeneration in the lateral and posterior columns.

In 1906 Barrett (2) reported the case of a woman with pituitary tumor, acromegaly, and degeneration of the posterior columns of the spinal cord in the cervical and upper dorsal regions. Beduschi (3) in 1907 reported the case of a patient with "the paraplegic form of acromegaly." In 1933 Barker (1) presented a patient with acromegaly and coexistent paresis of the musculature of the lower trunk and thighs.

All physicians who have observed patients with acromegaly are well acquainted with the fact that muscle weakness is a common feature of the condition and that it may become severe. Therefore, it has seemed possible to us that the underlying metabolic strain which is brought to bear upon the tissues in such patients might, if better understood, throw some light on the obscure etiology of some of the muscular dystrophies and perhaps neuropathies.

In man, great interest in the possible relationship of vitamin E to amyotrophic lateral sclerosis followed the work of Einarson and Ringsted (6). For a time there was high hope that a cure might be at hand. Early reports indicated an improvement rate of 20 or 30 per cent (7), but other reports suggested only a short-lived transitory effect (8). An attempt to cover the many clinical reports on the subject is not called for here. In general, it is evident now that the theory that vitamin E can be considered in any sense a cure for amyotrophic lateral sclerosis is untenable in the opinion of most observers. Vitamin E deficiency in many species of animals has been clearly shown to have as its most common manifestation necrosis of striated muscle. Associated lesions in the nervous systems of experimental animals have been reported, but the consensus of opinion seems to be clear that such lesions are not primary, and, according to the careful examination of the problem by Wolf and Pappenheimer (12), such damage is due to some factor other than vitamin E. A splendid review of the experimental evidence, besides those mentioned, is that of Mason (9).

## CASE REPORTS

*Case 1.* An Italian woman, aged 41, was first seen on July 15, 1933. Her family history was irrelevant. She had had 3 normal children, and her menses, which had begun at the age of 14, had remained normal. She had first noted enlargement of her head and hands following the birth of her last child eight years previously. This condition had become progressively worse during the past few years. Her presenting symptoms included frontal headaches experienced daily for seven years, profuse perspiration, and marked coarsening of the skin. For some years she had complained of constant hunger, increased thirst, and polyuria. In the preceding one and one-half years coarse hair had appeared on

her face. However, the paramount symptom was progressive weakness which had developed in her left arm six months prior to admission and which three months later had spread to involve her legs so that she rose from a chair and walked with great difficulty. For a period of one year there had been a sensation of twitching of the muscles over most of the body (Fig. 1).

On physical examination the blood pressure was 160 systolic and 88 diastolic; the pulse 110. The typical body configuration of acromegaly was evident at a glance. The pupils were equal and reacted, and the fundi were normal. There was no exophthalmos,

FIG. 1. *Case 1.* (a) Patient at age of 29. (b) Patient at age of 41, showing typical features of acromegaly.

nystagmus, or ocular muscle palsies. A large nodular goiter of rubbery consistency was present. The lungs were clear. The heart was rapid but regular, and there was a grade 2 systolic murmur at the base, although there were no signs of cardiac enlargement. The abdominal examination was normal. The neurologic examination revealed marked atrophy of both deltoid muscles as well as the muscles of the arms and forearms. Hoffman's sign was positive bilaterally, and fibrillary twitchings were present in the muscles of both arms. The Babinski sign was questionable bilaterally. The deep tendon reflexes were slightly exaggerated in both arms and both legs. Sensory perception was normal.

X-ray examination of the skull demonstrated an enlarged sella turcica. The visual fields were within normal limits. The basal metabolic rate varied from +35 per cent to +52 per cent. The glucose tolerance test curve was diabetic in type. There was free

hydrochloric acid in the stomach. The urinalysis was normal, and the blood count revealed a slight anemia with a hemoglobin (Haden-Hausser) of 12 Gm. and a leukopenia of 3500 white blood cells. The serum calcium was 11.2, phosphorus 4.4, and urea 33 mg. per 100 cc. The Wassermann and Kahn tests were negative.

At this point, and cognizant of the fact that acromegalics are poor surgical risks, it was decided to subject the patient to pituitary surgery. After iodine preparation a right frontal craniotomy was performed by Dr. W. James Gardner. The patient developed pneumonia and died on the fourth postoperative day. The autopsy revealed a pituitary adenoma of the acidophilic type and degenerative changes in the spinal cord consistent with the diagnosis of amyotrophic lateral sclerosis (Fig. 2).

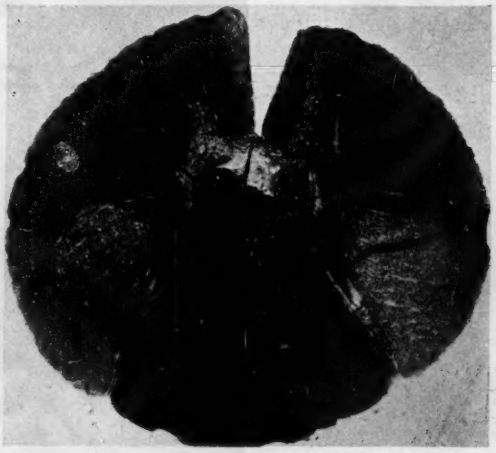

FIG. 2. *Case 1.* Dorsal spinal cord showing areas of demyelinization in the lateral and anterior funiculi. (Spielmeyer's myelin sheath stain) ×10. Identical changes were demonstrated in the cervical cord.

*Case 2.* An American woman, aged 66, was first seen on February 2, 1938. The family and past medical history were noncontributory, and a review of the special systems was negative. Her menses had always been normal, with natural menopause at the age of 50. Over the twenty years preceding admission she had noted gradual coarsening and enlargement of her features (Fig. 3). For ten years there had been considerable enlargement of the hands and feet, necessitating an increase in shoe size from 5½ to 8, and her gloves had to be especially made because of their large size. She had noted increased pigmentation of the skin and excessive perspiration. Approximately one year before admission she experienced soreness in her back following an automobile trip, and five days later her lower extremities became so weak she had difficulty walking. In retrospect she had noted fleeting indications of this difficulty for two or three years. When we saw her the weakness had progressed until she could not walk without assistance and had spread in the intervening few months to involve the muscles of the upper extremities as well. She could not raise her hands to feed herself or comb her hair, and as she lay supine she could not lift her feet from the bed.

Physical examination revealed the typical proportions of an acromegalic. The blood pressure was 160 systolic and 100 diastolic, the pulse rate 98. The skin was thickened, and there was hypertrichosis of mild degree. The skin was unusually dark. She perspired profusely and almost constantly. The pupils were equal, reacted normally, and the fundi, except for some arteriosclerosis of the vessels, were normal. There was no exophthalmos, lid lag, or ocular muscle palsy. No goiter was palpable. The heart, lungs, and abdomen were normal to physical examination. Neurologic examination revealed hyperactivity of

FIG. 3. *Case 2.* (a) Patient at age of 22. (b) Patient at age of 66. Skeletal changes, particularly about joints, apparent. Evidence of interosseous muscle atrophy, especially in left hand. Acromegalic facial characteristics are evident.

all the deep reflexes. Babinski's sign was positive on the left, and the abdominal reflexes were absent. There was marked atrophy of the muscles of the arms and legs, and a few fibrillary twitchings were visible. Sensory perception was normal.

X-ray examination showed ballooning of the sella turcica. Visual fields were within normal limits. The fasting blood sugar ranged from 117 to 152 mg. per 100 cc. Serum calcium was 10, phosphorus 4.1, and cholesterol 130 mg. per 100 cc. of blood. The blood sodium was 365 mg. (normal 330–355), and potassium 20.3 mg. (normal 16–22) per 100 cc. There was slight anemia with hemoglobin 10 Gm. per 100 cc. and eosinophilia 12 per cent. Creatinine and creatine values on twenty-four hour urine specimens were determined on frequent occasions from February 15, 1938, to April 9, 1938. The creatinine varied from 455 mg. to 1180 mg., creatine from 50 mg. to 811 mg. On April 9, 1938, the

twenty-four hour urinary creatinine was 1000 mg. and the creatine was 50 mg. The basal metabolism values were as follows:

| | | | |
|---|---|---|---|
| 2- 8-38 | +27 | 1-31-39 | +24 |
| 2-10-38 | +28 | 2- 4-39 | +39 |
| 2-15-38 | +15 | 2 -3-39 | +11 |
| 2-21-38 | +25 | 3-28-39 | +24 |
| 2-28-38 | +16 | 7-19-39 | +12 |
| 4- 7-38 | +30 | 9- 6-40 | − 0 |
| 4- 8-38 | +31 | | |

Muscle biopsies by Dr. B. S. Kline failed to reveal changes sufficient to be of diagnostic significance.

Our diagnosis included adenoma of the anterior lobe of the pituitary (acidophilic) with acromegaly, diabetes mellitus (mild), hypermetabolism with probable hyperthyroidism, and amyotrophic lateral sclerosis.

She was seen by three consultants in neurology. Two agreed to the diagnosis of amyotrophic lateral sclerosis. The third, Dr. S. Baumoel, dissented, pointing out that the course of the disease had not been so relentless as to permit such an unqualified neurologic diagnosis. In the light of subsequent developments his opinion seems to have been justified. The physical findings and the metabolic changes simulate those in *case 1* closely enough, however, to induce us to include the record here for comparison. We have chosen to classify her case as one of acromegaly of the amyotrophic type.

The patient was given vitamin $B_1$, 10 mg. three times a day, Lederle's liver extract, 1 cc. daily, Lugol's solution, 1 cc. three times a day for one month, and subsequently fifteen drops three times a day. The dose of liver and Lugol's solution was varied from time to time. Protamine zinc insulin, in doses approximating 10 units daily, as well as a relatively high protein diet was given. From February 21, 1938, until March 3, 1938, the patient was given x-ray therapy to the pituitary and thyroid glands. A total of 1000 r. was given over each temporal area and 1200 r. to the thyroid region.

It is a matter of interest to note that Lugol's solution in doses of 1 cc. three times per day did not result in any depression of the basal metabolic rate over a period of a month, and in smaller doses over a period of many months. This is a rather strong suggestion that factors external to the thyroid were important in the mechanism of increased oxygen consumption. It is also interesting that the radiation therapy administered over the thyroid and pituitary region apparently had no effect upon the basal metabolic rate.

Blood sugar estimations were made both fasting and postprandially on repeated occasions following the beginning of insulin injections and were always found to be normal. Approximately one year later the patient reported that she felt stronger. No fibrillary twitching was seen at that time, and the reflexes were less active. Babinski's sign remained positive on the left. Improvement continued steadily, and in 1940 she was given vitamin E (Ephynal made by Hoffmann-LaRoche) in addition to other medication. In 1946, eight years after we first saw her and at the age of 74, she is able to do her own housework, walk unassisted upstairs, and work in her garden. (A recent examination showed an easily exhausted Babinski sign on the left.)

*Case 3.* A man, aged 52, was first seen on April 22, 1946. He had been aware of an increase of skin coarseness and enlargement of the head and extremities quite typical of acromegaly for the past five or six years. His chief complaint at admission was, however, progressive weakness in both lower extremities for a three-year period prior to this time. He described his legs as "feeling like rubber," and for the three weeks before admission

he had been unable to stand by himself. He noted that his legs were smaller, flabbier, and that the muscles twitched at times. He had no weakness of the upper extremities. There was no headache or visual disturbance. He was irritable and had felt unusually depressed recently, and sexual libido had disappeared. The past history, the family history, and the systemic review were noncontributory. He had 1 child alive and well. Physical examination revealed a blood pressure of 120 systolic and 80 diastolic and a pulse rate of 84. His appearance was typical of severe acromegaly. The pupils were active and equal, and the fundi were normal. The submaxillary, digastric, and anterior cervical glands were slightly enlarged. The thyroid was not palpable. The chest was barrel-shaped, and the lungs were clear. Extreme dorsal kyphosis was present. The heart was normal, and no murmurs were present. The external genitalia were normal. There was marked atrophy and weakness of both legs, most prominent on the right. Fibrillary twitchings were visible in both thighs. Babinski's sign was negative. The deep reflexes were 3+hyperactive except for the right ankle and knee jerk, which were 2+hyperactive. There was no ataxia, and the abdominal reflexes were present over the upper half but absent over the lower half of the abdomen. Photographs were not permitted.

X-ray examination of the skull demonstrated an enlarged sella turcica with smooth contour. The visual fields showed an enlargement of the blind spot on the right eye. The water excretion test (Robinson, Power, Kepler) gave an index of 51.5. Semen examination showed 10,800,000 sperm per cc., a total count of 41,040,000, of which 95 per cent were nonmotile. Urinary gonadotropins measured slightly more than 105.6 mouse units per twenty-four hours. The urinary 17-ketosteroids (ketonic fraction) were 7.3 mg. per twenty-four hours (normal 7–14).

The possibility of deformity of the skull or of the cervical or dorsal regions of the spine as a cause of the neuromuscular changes was seriously considered. Roentgenograms were carefully reviewed with neurosurgeons and radiologists, and those who saw them believed that such an explanation was not valid.

The diagnosis lay in a choice between acromegaly and amyotrophic lateral sclerosis versus acromegaly of the amyotrophic type.

In an attempt to encourage nitrogen retention in the muscles, testosterone propionate 25 mg. every second day and a diet containing 125 Gm. of protein per day were given. One month later the patient reported that he felt stronger generally, though his legs were not definitely improved. Two months later he claimed to be stronger and could walk unsupported, though with much difficulty, and could drive his own automobile, which he had previously been unable to do.

Shortly afterward he died suddenly following a cerebral vascular accident. Autopsy was not obtained.

## SUMMARY

One patient with acromegaly and proved amyotrophic lateral sclerosis is reported. Two patients with acromegaly are reported in whom a clinical diagnosis of amyotrophic lateral sclerosis was strongly suspected. Treatment designed to normalize the metabolic state was followed by slow but pronounced improvement in one. In the other, in a period of less than three months' therapy, suggestive but unconvincing evidence of recovery was seen.

It is suggested that in these patients the increased metabolic demand incident to the acromegaly was an important factor in the production of

the neuromuscular disease which simulated or actually was amyotrophic lateral sclerosis.

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# CONJUNCTIVAL AND CORNEAL LESIONS IN HYPERCALCEMIA*

FRANK B. WALSH AND JOHN EAGER HOWARD

*From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and the Department of Medicine of the Johns Hopkins University and Hospital*

THE hypercalcemia, which accompanies certain disease states and may be the clue to the diagnosis of the underlying pathological physiology, is often overlooked by the clinician. The reasons for this are not far to seek, since the symptoms referrable to hypercalcemia per se are usually nondescript and common to many disease patterns—namely, fatigue and vague muscle and bone pains, nausea with or without vomiting, and polyuria (1). In the past few years we have observed, in approximately one-half the patients with hypercalcemia, distinctive phenomena in the eyes which are believed to be the direct result of the hypercalcemia. These observations, together with a brief discussion of the possible mechanism of their production and of their diagnostic value, form the basis of this report.

## DESCRIPTION OF LESIONS

Two distinct types of ocular abnormalities have been observed; one in the conjunctiva, the other in the cornea. Neither can be identified except with the aid of the slit lamp. The conjunctival lesions appear as small glass-like particles (Fig. 1) within the conjunctiva of the palpebral fissure region. These minute areas are crystal clear, and not at all like the grayish patches sometimes seen extending superficially over a pterygium. The lesions may be many or few. Sometimes there is accompanying redness of the conjunctiva with complaint of conjunctival irritation; the latter may even be the patients' most annoying symptom. In two instances biopsies of the lesions have been obtained. The amount of tissue obtainable was, of course, very minute. Microscopic sections were made from one bit of tissue and chemical analysis was performed on the other. The deposits were identified by a member of the Johns Hopkins University Department of Chemistry as "probably calcium phosphate." The patient suffered from hyperparathyroidism. This determination was made six years ago, and we have no way now of finding out what methods were used in identification. Furthermore, the note states that "there were many technical difficulties involved." Microscopic sections taken from the other biopsied specimen,

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which was removed from a patient with vitamin D poisoning, are depicted in Figures 2 and 3. Dr. Richard H. Follis' description of these follows:

"The epithelium in general is normal. Just beneath the basal layer and lying in the most superficial connective tissue, there is purplish staining amorphous material which is more refractile than the rest of the tissue. There is no cellular reaction about this material. With the Von Kossa silver stain this material stains an intense black and is found to be granular and to be present in larger quantity than was suspected with the H and E stain. In most of the sites of deposition of this material, the overlying epithelial cells are entirely normal. However, in several areas, where the

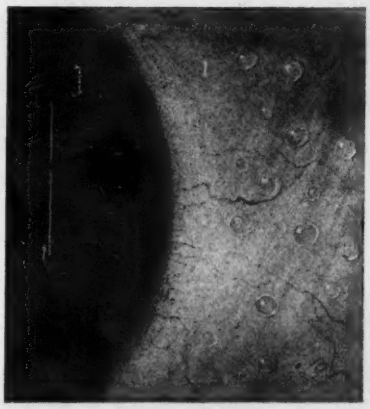

FIG. 1

silver staining substance is greatest, the basal epithelial cells show vacuolization."

The second type of ocular abnormality observed occurs in the cornea. The corneal changes (Fig. 4) consist of hazy grayish granular epithelial and subepithelial opacities running concentrically with the limbus, on either the nasal or temporal side or both. The opacity is most dense at the periphery, fading out centrally, but may faintly involve almost the entire cornea. Its appearance is quite similar to that of band keratitis which is ordinarily seen in association with intraocular inflammation and is familiar to all ophthalmologists. There is, however, a single difference; in the corneal lesion here described there are clear areas within the area of opacity. Band keratitis which is occasionally reported as a primary disorder is extremely rare. "Primary" band keratitis may be progressive and seriously affect vision. Its etiology is unknown and it well may be that some such cases may have been due to hypercalcemia. The corneal involvement associated

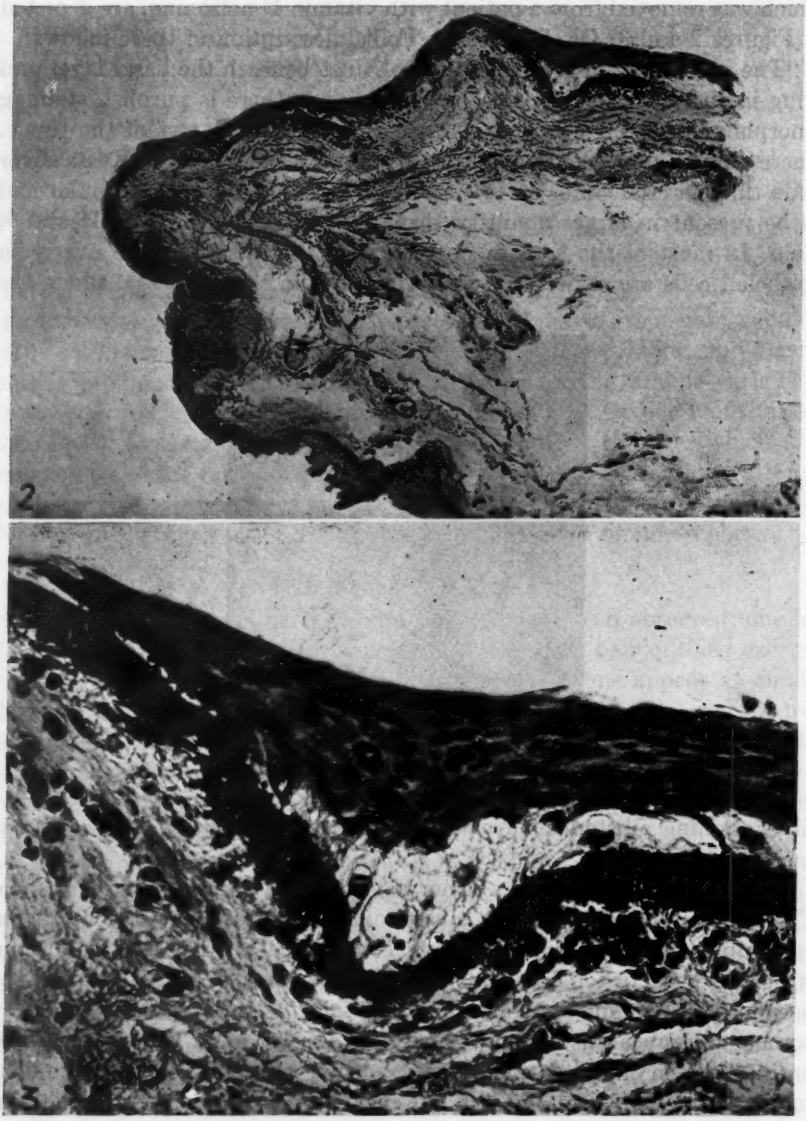

FIG. 2 and 3. *Case #414730* Biopsy of conjunctiva. Tissue immediately placed in neutral formalin (formalin 10% saturated with magnesium carbonate). Pieces were imbedded in paraffin, sectioned and stained with von Kossa technique. Fig. 2.—×100 magnification. Fig. 3.—×450 magnification.

with hypercalcemia should not be confused with arcus senilis since the opacities are much more superficial. Also the lesions are easily distinguished from the white limbus girdle described by Vogt.

## ANALYSIS OF CASES

Over the 10-year period since the first conjunctival lesion of this type was noted, it has been possible for us to examine by slit lamp 20 patients suffering with elevation of the serum calcium. In eight instances calcium depositions in the conjunctiva were found; there were five instances of

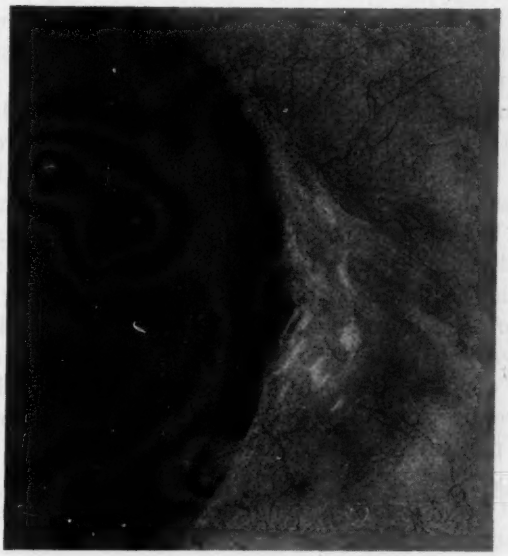

FIG. 4

band keratitis in our series, and in all but one there were also present conjunctival lesions. Since 1940 ocular lesions have been looked for in hypercalcemic patients at the Massachusetts General Hospital, and seven instances of the band keratitis lesions have been encountered. As yet no conjunctival lesions have been observed by them. We have Dr. David Cogan's permission to include his findings in this report (2) and the combined cases will be discussed as a whole. Thus there have been seen to date 16 patients with distinctive ocular lesions of these two types in hypercalcemic patients, 12 corneal, eight conjunctival (five having lesions of both types). In hundreds of patients examined by one of us (Walsh) with the slit lamp during the last 10 years, no patient without hypercalcemia has shown conjunctival depositions of the kind described above. Since band

keratitis lesions of the so-called idiopathic type (i.e., without intraocular inflammation) are extremely rare, the occurrence of 12 instances of such lesions in patients with hypercalcemia is striking. It would seem that the ocular lesions in both these types are definitely related to, and probably the result of, hypercalcemia.

## TYPES OF CASES IN WHICH THE OCULAR MANIFESTATIONS OCCUR

Conjunctival deposits have been seen associated only with hyperparathyroidism and poisoning from vitamin D. Concentration of calcium in the serum of these patients has ranged from 12 to 19 mg. per 100 cc. Cases with vitamin D poisoning all had concentrations of serum inorganic phosphorus of 3.5 mg. per 100 cc. or greater. Only one such case was without evidence of serious renal damage from the drug; the others all manifested albuminuria and casts, elevated non-protein nitrogen in the blood, with impaired ability to form concentrated urine and to excrete phenolsulfonphthalein. The patients with hyperparathyroidism without serious renal impairment had low concentration of inorganic phosphorus in the serum (Table I). In three instances the appearance of the conjunctival deposits has changed markedly after the hypercalcemia has been corrected. One of these, a patient suffering with mild vitamin D poisoning without noteworthy renal complications, showed only a few of the crystalline deposits in the conjunctiva; when observed four months later with normal serum calcium, the deposits had entirely disappeared. A physician with hyperparathyroidism and renal insufficiency had many conjunctival deposits prior to parathyroid surgery; two years later, during which interval mild hypoparathyroidism had been present, all but a few of the conjunctival lesions had disappeared despite progression of renal insufficiency and the development of hypertension.

Another case is worthy of special comment. This patient had for many years suffered with hypocalcemic tetany, probably due to a combination of deficiency of vitamin D further enhanced by hypoparathyroidism after thyroidectomy. She was given 250,000 units of calciferol daily for 15 days. Serum calcium and phosphorus altered with unexpected rapidity from 7.7 mg. and 3.4 mg., respectively, per 100 cc. to 15.8 mg. and 4.3 mg. Routine slit lamp examination had been performed just prior to calciferol administration with negative findings. On the 15th day when signs of vitamin D poisoning became apparent, there were readily visible characteristic conjunctival lesions. The patient left the Johns Hopkins Hospital and was followed thereafter by Dr. Milton F. Little. Two weeks after the lesions had appeared, they were seen to be still present. Five months later reexamination by Dr. Little showed that the lesions had entirely disappeared.

TABLE I

| History No. Sex | Age | Diagnosis | Ca mg. % | P mg. % | NPN mg. % | Prot. Gm. % | Ocular Lesions |
|---|---|---|---|---|---|---|---|
| J.H.H. F | 168084 40 | Vitamin D poisoning | 13.6 | 3.9 | 46.0 | 7.0 | Crystals in bulbar conjunctivæ. |
| J.H.H. F | 421206 62 | Vitamin D poisoning | 15.1 | 5.2 | 75.0 | 6.6 | Conjunctival crystals and band keratitis, bilateral. |
| J.H.H. F | 414730 59 | Vitamin D poisoning | 14.9 | 3.5 | 57.0 | 7.0 | Conjunctival crystals and band keratitis. |
| J.H.H. F | 366421 36 | Vitamin D poisoning | 15.8 | 4.3 | 23.0 | 7.1 | Conjunctival crystals appeared within 10 days. |
| J.H.H. M | 419594 54 | Vitamin D poisoning | 13.6 | 4.6 | 89.0 | 6.7 | Conjunctival crystals and band keratitis, bilateral. |
| J.H.H. M | 204618 31 | Hyperparathyroidism | 12.7 | 7.3 | 82.0 | 6.8 | Conjunctival crystals and band keratitis, bilateral. |
| J.H.H. M | 190342 49 | Hyperparathyroidism | 19.3 | 4.3 | 90.0 | 6.3 | Conjunctival crystals. |
| J.H.H. M | 194939 59 | Vitamin D poisoning | 14.3 | 4.6 | 68.0 | 7.0 | Band keratitis. No conjunctival lesions. |
| J.H.H. F | 224565 31 | Hyperparathyroidism | 13.6 | 1.7 | 36.0 | 7.0 | Conjunctival crystals. |
| M.G.H. M | 324826 49 | Hyperparathyroidism | 12.4 | 6.6 | Elevated | — | Abortive band keratitis. Conjunctival calcification. |
| M.G.H. M | 268258 25 | Hyperparathyroidism | 12.3 | 4.8 | Elevated | — | Narrow strip in corneal limbus. |
| M.G.H. M | 391430 25 | Sarcoid ? beryllium poisoning | 15.6 | 3.1 | 26.0 | 6.7 | Chalk-like opacities of limbal corneae. |
| M.G.H. M | 235557 44 | Hyperparathyroidism | 12.0 | 4.7 | 132.0 | 8.6 | Band keratitis. |
| M.G.H. F | 252484 36 | Sarcoid | 14.4 | 4.1 | 75.0 | 7.0 | Abortive band keratitis. |
| M.G.H. M | 254784 27 | Vitamin D poisoning | 12.6 | 4.3 | 52.0 | 5.6 | Abortive band keratitis. |
| M.G.H. F | 589 59 | Hyperparathyroidism | 12.4 | 2.4 | 23.0 | 6.2 | Abortive band keratitis. |

In the Johns Hopkins series of hypercalcemic cases examined by slit lamp, there have been five proven instances of hyperparathyroidism in which neither type of ocular lesion was manifest. Six patients, who were suffering from multiple myeloma, sarcoid or skeletal carcinomatosis, have been examined; none thus far have manifested either type of ocular lesion, nor have uremic cases with normal serum calcium and high serum phosphorus concentrations. However, Cogan has seen two instances of band keratitis in patients with hypercalcemia in association with sarcoid.

The keratitic lesions have appeared five times in the Johns Hopkins series, in four patients with vitamin D poisoning and renal insufficiency, in one patient with hyperparathyroidism who also had renal insufficiency. When first seen, serum calcium levels in the vitamin D cases were 13.6 mg. or higher per 100 cc., with phosphorus 3.5 mg. or above. The hyperparathyroid patient's serum calcium was 13.2 mg., phosphorus 3.8 mg. (he suffered also with renal insufficiency). Of Cogan's seven cases, only one suffered with vitamin D poisoning, four had hyperparathyroidism (one with low serum phosphorus without renal insufficiency, the other three with elevated non-protein nitrogen and serum phosphorus) and two patients had sarcoid. The serum calcium concentration in this group varied from 12.0 to 15.6 mg. per 100 cc.

## DISCUSSION

We are not, at this time, informed as to the exact nature of the lesions here reported. It has been assumed that the lesions seen in the conjunctiva with the slit lamp as refractile glass-like particles are, in fact, the subepithelial basophilic deposits so clearly outlined by the silver stain in the biopsy specimen. The pathological specimen demonstrated that the size of the areas is of the correct order, and the deposits lie just beneath the epithelial layer, both facts which make the assumption more tenable. The clinical lesions have never been seen by us or our colleagues in patients who did not have hypercalcemia, but a study of conjunctival biopsies is now in progress, designed to determine if pathological lesions of this sort occur in normal or other disease states.

It is also entirely an assumption that the material in the lesions is calcium and that the salt is phosphate. The staining reaction is not altogether specific. By all odds the cation most likely to have been present in such a situation, however, is calcium; and the single specimen chemically analyzed lends strong corroboration. The hypercalcemic state (presumably higher than normal ionized and diffusible calcium) is the only factor common to all the patients, so far as we have been able to discern. Certainly the variations in serum concentration of phosphorus in this series were great, from levels of 7.3 mg. per 100 cc. to low levels in the uncomplicated cases of hyperparathyroidism.

We are equally lacking in knowledge as to why the calcium salt, if such it be, is deposited in the conjunctival basement membrane, and whether or not it is a deposit of the same salt beneath the surface epithelium of the cornea which causes the band keratitis. It may be that, since basement membranes in general are basophilic, the ocular lesions are but visible manifestations of deposits in many basement membranes under metabolic conditions similar to the ones met with in these patients (3). Certainly

deposits in the basement membranes of the renal tubules in hypercalcemia and alkalosis have a similar appearance.

We are wont to classify pathological calcification into two groups: 1) In one group are those cases in which it appears likely that a local process, usually degenerative, has produced changes conducive to the deposition of lime salts; in this group are the calcific lesions seen in the fat necrosis after leakage of pancreatic juice, calcification in arteriosclerotic plaques, in muscles after some hemorrhages and myositis ossificans, and the lesions of so-called idiopathic calcinosis. 2) The other group includes disease states which are accompanied by changes in the concentrations of ionized calcium or inorganic phosphorus, or both, in the serum. Examples of this type are vicarious calcification seen in chronic alkalosis, certain cases of renal insufficiency, hyperparathyroidism and vitamin D poisoning.

The ocular lesions herein described would seem clearly to fall within the latter group. There must, however, be some factor other than hypercalcemia, as yet unknown, in the production of these ocular lesions, for they have not been observed in *all* patients with vitamin D poisoning or hyperparathyroidism, and in our small group we have not been able to correlate the degree of elevation of serum calcium nor the duration of the pathological state with their appearance.

It is hoped that further studies will aid in elucidating some of the mechanisms of calcification, still so poorly understood. Recognition of such lesions by ophthalmologists and other clinicians may also serve as an important clue to diagnosis of patients with hypercalcemia, in whom the fundamental pathological physiology might not have been suspected otherwise.

## SUMMARY

Ocular lesions of two types, identifiable only by slit lamp examination, have been observed in patients with hypercalcemia. In one type there are small glass-like particles in the conjunctiva of the palpebral fissure area. Biopsy of one of these lesions showed a deposit of amorphous material, presumably a calcium salt, beneath the conjunctival basement membrane. Eight examples of this ocular abnormality are reported among 20 patients with hypercalcemia examined.

Associated corneal lesions have been observed in four of these cases, and an additional seven have been seen by Cogan and his associates at the Massachusetts General Hospital. The corneal changes consist of hazy grayish granular epithelial and subepithelial deposits running concentrically with the limbus on either the nasal or temporal side or both. These are quite similar to band keratitis, a picture familar to ophthalmologists.

The only metabolic abnormality common to the entire group with these two types of ocular lesions has been hypercalcemia. The lesions have been

observed in hyperparathyroidism, vitamin D poisoning and twice in patients with sarcoid. The lesions have been associated with both very high and very low concentrations of serum phosphorus. In two instances the conjunctival lesions have disappeared after the hypercalcemia was corrected. So far the corneal lesions have not been observed to disappear.

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# PREGNANCY TEST USING THE MALE TOAD

CARLOS GALLI MAININI

*From the Service of Endocrine Diseases of the Rivadavia Hospital, Buenos Aires, Argentina**

IN THIS report a new pregnancy test is described, in which the male toad (*Bufo arenarum Hensel*) is used as the reacting animal.

The positivity or negativity of the test is determined by the presence or absence of spermatozoa in the urine of the toad previously injected with the urine of a woman suspected to be pregnant.

The spermatozoa of the adult toad are in contact with the Sertoli cells and are grouped together, parallel to each other, in such a way that they appear like bundles. Occasionally the spermatozoa are free and detached from the wall of the tubes and can be seen as a loose skein.

The relation between the pituitary and the testis of *Bufo arenarum Hensel* has been studied by Houssay and Lascano Gonzalez (2). These authors found evidence that in the toad the pituitary exerts a constant influence upon the spermatogenetic activity of the testis, and that removal of the pituitary produces testicular atrophy. Repeated subcutaneous implantation of toad pituitary caused testicular hypertrophy in normals and pituitarectomized animals.

The administration of toad pituitary to the toad produces the detachment of the spermatozoa, which appear free in the interior of the tubes. The phenomenon of the detachment of the spermatozoa and their migration through the kidney has been well studied by De Robertis, Burgos and Breyter (3) in the *Bufo arenarum Hensel*. Following their detachment the spermatozoa migrate to the bladder and are excreted with the urine.

Based on the results shown in this report, the pregnant woman's urine also has the property to induce the detachment and migration of the spermatozoa, which, some time after the injection, can be found in the urine contained in the bladder.

The results here presented are comparable to those obtained in the rabbit, because in every case, simultaneously with the reaction in the toad, a Friedman test was performed using the same pregnant woman's urine.

## METHODS

**Test animals:** Toads weighing more than 100 grams were used. Toads of less than 100 grams are apt to have incomplete spermatogenesis. The

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* Chief: Dr. Enrique B. del Castillo, Buenos Aires, Argentina.

majority of toads were recently captured. Others had been in captivity more than one month. In some reactions, toads injected one week before were used again.

**Urine injected:** 10 cubic centimeters of the first morning specimen of urine from the suspected pregnant woman was injected into the lateral lymphatic sac of each toad. The urine was not subjected to any special previous preparation (filtration, pH, concentration, etc.). All the injections were made during the morning. From that time on the toads were kept in their basins or cages. No special illumination was used, the toads being kept under the natural light of the laboratory. Simultaneously, a Friedman test was performed with urine taken from the same sample, for the purpose of determining the coincidence of the two tests. The Friedman reactions were carried out independently by other investigators.

**Procurement of urine samples from the toad:** The urine was obtained from the toad by introducing a pipette into the anal canal. The pipettes used are of variable gauge, approximately the same as the ones of one cubic centimeter. To collect the urine the toad is dorsally held on the table, the pipette is introduced no deeper than 0.5 or 1 cm. in the anal canal and is gently moved back and forward until a drop of urine is seen to penetrate the pipette. It is of importance, when the pipette is introduced into the canal, that the end of the pipette be held upwards. This position of the pipette facilitates the collection of the urine. No more than a drop is necessary. By extracting this small amount the bladder is not emptied, and, if necessary, subsequent samples can be collected.

**Microscopic observation:** A drop of the urine thus obtained is placed on a slide and observed directly under the microscope without previous smearing, fixing or staining. A strong illumination is not necessary. The spermatozoa are seen in great quantities as delicate undulating short dark lines.

**Time of observation:** Most of the toads' urines are examined 1, 2, 3 and 22 hours after the injection of woman's urine. In order to determine how long a positive reaction shows spermatozoa in the toad urine, some observations were made until 3 days after the injection.

**Season of the year:** These experiments were performed during the months of January and February, 1947, that is to say, during the summer months.

## RESULTS

| | | |
|---|---|---|
| Total number of reactions | | 102 |
| Deaths due to the injection | toad | 1 |
| | rabbit | 2 |
| Comparable results | | 99 |
| Consistent results | | 94 |

| | | | |
|---|---|---|---|
| Inconsistent results | toad positive—rabbit negative | 3 | |
| | rabbit positive—toad negative | 2 | |
| Positive results | | | 62 |
| Positive results observed at 1, 2, 3 hours after injection | | | 47 |
| Positives after 1 hour | | 9 | |
| Positives after 2 hours | | 36 | |
| Positives after 3 hours | | 2 | |
| | Total | 47 | |
| Positive results observed during 3 days | | | 18 |
| Maximum time that spermatozoa could be found in the urine of these 18 toads after injection | | | 50 hours |

**Control experiments:** As a control of this reaction, the urine of 77 different subjects and several substances were injected. The 77 urines tested gave uniformly negative results. The urines injected were obtained from:

Children: 5 males, 10 females.
Normal adults with active sexual life: 18 men, 20 women.
Women at menopause: With symptomatology 6; without symptomatology 5.
Men above 60: 4.
Thyrotoxic adult women: 4.
Secondary amenorrhea: 3.
Hirsutism: 2.

**Other substances:** Other substances were injected as controls. The following enumeration shows the name of the substance injected along with the dose per toad, the number of toads used and the results obtained. In every case the dose was given in one injection and observations were made within 3 hours and at 24 hours after the injection.

| | | | |
|---|---|---|---|
| Estrogens: 10,000 U. estradiol benzoate | | 12 toads | negative |
| 1 mg. stilbestrol | | 14 toads | negative |
| Progesterone: 5 mg. | | 5 toads | negative |
| Testosterone propionate: 10 mg. | | 6 toads | negative |
| Thyroxin: 1 mg. | | 5 toads | negative |
| Insulin: 2 units | | 6 toads | negative |
| Adrenaline: 0.5 cc. (1:1000) | | 10 toads | negative |
| Desoxycorticosterone Acetate 10 mg. | | 6 toads | negative |
| Chorionic Gonadotropin: 1–10 U. | | 5 toads | negative |
| | 100 U. | 3 toads | Positive 1 hour |
| | 500–1000–1500 U. | 8 toads | Positive 30 minutes |
| Serum Gonadotropin: | 500 U. | 12 toads | 4 Positive 2 hours |
| | | | 4 Positive 22 hours |
| | | | 4 Negative 48 hours |

**Temperature:** The influence of this factor was studied by injecting 500 U. of chorionic gonadotropin per toad, into 12 toads kept for 22 hours at different temperatures. The rectal temperature of each toad was meas-

ured at the end of the 22 hour period, when the gonadotropin was injected. Of the toads with an average temperature of 26° C., 3 were positive 30 minutes after the injection and all at one hour. Of the toads with an average temperature of 16° C., only one was positive at 30 minutes, and all at one hour. Of the toads with an average temperature of 9° C., no one was positive at 30 minutes, 4 were positive at one hour, and all one hour and 45 minutes after the injection.

## DISCUSSION

Based on the results reported, it seems that the urine of pregnant women has the property of producing the detachment and migration of the toad's spermatozoa. The negative results, obtained with the control substances injected—with the exception of chorionic and serum gonadotropins—and the consistency of results with the ones obtained when performing the Friedman tests, suggest that the substance responsible for the reaction is the gonadotropin produced by the placenta.

Under the conditions in which these experiments were performed (season of the year, temperature, etc.) it can be concluded that this pregnancy test has the following advantages:

1. **Speed of the reaction:** All 47 positive reactions observed at 1, 2 and 3 hours were positive within 3 hours (9 in one hour, 36 in two, and the remaining 2 in three hours). The reactions which were negative at three hours remained so at 24 hours.

2. **Simplicity:**

(a) No special preparation of the urine to be injected is needed.
(b) The injection is without difficulties.
(c) The collection of the toad's urine is simple and no surgical intervention is needed.
(d) The microscopic observation is immediate, without previous histological procedures.
(e) The microscopic differentiation of spermatozoa is simple because of their number and well-defined characteristics of morphology and movement.
(f) The several steps of the technique can be performed rapidly. Usually one observation will not take more than one ninute from the moment that the toad is taken from the cage until the result is established.

3. **Clear end-point:** The positivity of the reaction is clearly indicated by the presence of spermatozoa in the toad's urine.

4. **Specificity:** Based on the results obtained with the control urines, this reaction is specific for pregnant women's urine.

5. **Economy:** The economy of the procedure is due not only to the low cost of the toad, but also because no special care is needed, i.e., food, handling, etc. In addition, the same toad can be used again after an interval of one week between reactions. The real practical value of this reaction is not definitely established by the data presented in this paper because of the

small number of urine examinations and because it might happen that the reaction of the toad could be different during other seasons of the year, i.e., during the mating period or variations of temperature. It would be of general interest to know if this reaction for the *Bufo arenarum Hensel* is also true for other species.

The species difference in this type of gonadotropic reaction is clearly demonstrated by the impossibility of producing ovulation in the female *Bufo arenarum Hensel* by the injection of pregnant woman's urine, a fact clearly established for the *Xenopus Laevis* by Shapiro and Zwarenstein in 1934 (4).

## CONCLUSIONS

1. The injection of 10 cubic centimeters of pregnant woman's urine is followed by the appearance of spermatozoa in the urine of the toad *Bufo arenarum Hensel.*

2. Of 99 pregnancy tests simultaneously performed in the toad and in the rabbit, 94 results were consistent. Of the remaining 5, 3 toads were positive, and 2 rabbits were positive.

3. In 47 positive reactions observed, spermatozoa appeared in the toad's urine within 3 hours after the injection. The negative results during this time were still negative after 24 hours.

4. In a group of 18 toads, once the spermatozoa appeared in the urine, it was possible to observe spermatozoa for a maximum of 50 hours.

5. Seventy-seven urines from non-pregnant subjects gave negative results.

6. The individual injection of certain doses of estrogens, progesterone, testosterone, thyroxin, insulin, adrenaline, and desoxycorticosterone were without effect.

7. The injection of individual doses of 100, 500, 1000 and 1500 I.U. of chorionic gonadotropin gave positive results, and the injection of 500 I.U. of serum gonadotropin gave some positive results.

8. Temperature seems to be a factor of importance in the speed of the reaction.

9. Under the conditions in which these experiments were performed (season of year, temperature, etc.) the results obtained are stimulating and could be the base for a new pregnancy test. The characteristics of this test can be summarized as follows:

A. Speed of the reaction
B. Simplicity
C. Specificity
D. Clear end-point
E. Economy

SUMMARY

A new pregnancy test is described in which the male toad (*Bufo arenarum Hensel*) is used as the test animal.

The injection of urine from a pregnant woman has the property of producing the migration of the spermatozoa from the testicles of the toad to the bladder. The spermatozoa can be observed under the microscope in a drop of toad's urine obtained by catheterization.

Ninety-nine comparative results with the Friedman reaction simultaneously made, and the results of 86 control experiments are shown.

Under the conditions in which this study was made, this pregnancy test has the advantages of speed of the reaction, simplicity, specificity, clear end-point, and economy.

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# Letter to the Editor

To the Editor:

## AN OBSERVATION ON MENSTRUAL MISBEHAVIORS

THE normal functions or balance of the glands of internal secretion, or the endocrine system, are subject to extraneous influences.

Shortly after returning to private practice from military service, one of the observations that struck us most forcibly was the large number of menstrual misbehaviors, either irregular cycles or dribbling or excessive flow in many of the younger patients seen. The probability of there having occurred during the war years sufficient stress, strain, anxiety, and emotional disturbance to produce a glandular imbalance seemed not unlikely.

With this in mind, and with the observation of an apparent preponderance of menstrual disturbances in younger individuals, it was felt that a study comparing a pre-war year with the last year of war might reveal some difference in the incidence of menstrual disorders. For this purpose, records were chosen for the years 1940 and 1945. Those individuals within the age groups from 19 to 39 only were considered. The only menstrual disorders recorded in the study were those diagnosed as menorrhagia, metrorrhagia, and dysmenorrhea. The findings were borne out by pathological reports of scrapings. If there was any question of pregnancy, such cases were eliminated. Likewise, fibroid growths and other pathological processes of the pelvis were eliminated as far as possible. In other words, only the actual functional disturbance of menstruation was recorded in this study.

Figures were obtained from two of the metropolitan hospitals in the city of Dallas for the pre-war year 1940, at which time there was a total of 82 cases of menstrual misbehavior of the type mentioned between the ages of 19 and 39, and a total of all-age admissions of females of 9,141. In 1945, which represents the cumulative effect of "war nerves," there was a total of 368 menstrual disorders amongst a population of all-age admissions of 12,398. These figures were tested for their significance. The difference in proportions of the two years was taken as indicated by the mathematics shown at the top of the next page.

The standard error of the difference was thus computed, which was found to be .0019. The difference in proportion divided by the standard error of the difference, which is considered a formal significance test, is 11 times the standard error of difference. Biometrically, any difference that is greater than twice the standard error is considered significant; that is, it is considered not to be a result of chance observation.

TABLE I. BASIC DATA

| | Total Admissions | Functional Menstrual Disorders |
|---|---|---|
| 1940 | 9,141 | 82 |
| 1945 | 12,398 | 358 |

Biometric Analysis

| | + | − | Total | Proportion |
|---|---|---|---|---|
| 1940 | 82 | 9,059 | 9,141 | .0090 |
| 1945 | 368 | 12,030 | 12,398 | .0297 |
| Total | 450 | 21,089 | 21,539 | .0209 |

Difference in proportion + = .0297 − .0090 = .0207

$$\text{Standard Error of Difference} = \sqrt{\frac{(.0209)\ (.8791)}{9141} + \frac{(.0209)\ (.8791)}{12398}}$$

$$= \sqrt{\frac{.018373}{9141} + \frac{.018373}{12398}}$$

$$= \sqrt{.00000201 + .00000148}$$

$$= \sqrt{.00000349}$$

$$= .0019$$

$$\frac{\text{Difference}}{\text{Standard Error of Difference}} = \frac{.0207}{.0019} = 11$$

The observation, therefore, leads one to feel that the four years of war tension played a rather striking role in traumatizing the glandular balance resulting in an endocrine imbalance as judged by the increased incidence of menorrhagia, metrorrhagia, and dysmenorrhea. We are certainly cognizant of other possible variables that doubtless contributed to this finding, but feel that the most important factor or factors were the results of the anxiety state that was admittedly present among the daughters, wives, or sweethearts of the men who were serving in the Armed Forces, to say nothing of the general and over-all effect on the population and its social fabrications.

It is hoped that this observation will be duplicated in some other hospitals in order to see if the same results are noted. Such knowledge adds

immeasurably, should it prove to be true, to our concept and increasing knowledge of psychosomatic medicine or functional disturbances in general. Its implications, further, as to the possible care and therapeusis for such conditions, both in individual peacetime care of the patient or in the presence of another holocaust would likewise be informative.

J. Shirley Sweeney
A. E. Haley and Leona Yaklin
Fort Logan Veterans' Hospital
Denver, Colorado
April 28, 1947

The senior author (J.S.S.) wishes to acknowledge with thanks the help of Lowell J. Reed, Vice President of Johns Hopkins University, in making the biometric analysis included in this study.

# Book Review

Riddle, Oscar and Associates. *Studies on Carbohydrate and Fat Metabolism. With Especial Reference to the Pigeon.* Washington, D. C. Carnegie Institution of Washington (Pub. 569).

This volume provides information on hitherto little-known aspects of the physiology of the pigeon, and places in relief the relatively few observed differences in mechanisms for the regulation of carbohydrate and fat metabolism in birds and mammals. The various investigations deal especially with the role of the several hypophyseal hormones in the regulation of blood sugar, ketosis, muscle and liver glycogen, heat production, plasma fat, and liver fat. Tests with hypophyseal hormones were supplemented by tests with insulin, thyroxin, sex steroids, and hormones of the adrenal cortex. Rabbits and rats, in addition to pigeons, were used in some of these studies. The action (and assay) of pituitary extracts obtained by fractionation with ammonium sulfate was studied extensively, and the results fully related to those of previous investigators in the field. Supplementing the use of intact pigeons, several hundreds of tests were made on birds from which one or another hormone-producing gland was removed—namely, thyroids, pancreas, one or both lobes of the pituitary, testes, ovaries, adrenals, and parathyroids. Cyclic glycemias and lipemias associated with egg production in pigeons and doves were found; and some evidence is reported which supports the view that hormones of the adrenal cortex and ovary, respectively, induce this cyclic fluctuation of these two substances in the blood.

# ANNOUNCEMENT OF THE 1948 MEETING OF THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

The Thirtieth Annual Meeting of the Association for the Study of Internal Secretions will be held in the Palmer House, Chicago, Illinois, June 17 and 19, 1948.

The scientific sessions will be held in the Red Lacquer Room and registration will be on the fourth floor just outside the Red Lacquer Room. The Annual Dinner will be held in the same room on Friday, June 18th at 7 P. M. and will be preceded by a cocktail party, the location of which will be announced later. The Council will meet at 2 P. M. Thursday, June 17th.

All members of the Association who plan to attend the Thirtieth Meeting are urged to make their reservations at once with the Palmer House, stating the time of arrival and how long they plan to remain in Chicago.

# Announcement of Awards and Fellowship of the Association

*Nominations for Awards*

Three awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. A special committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council, and each member of the Association has the privilege of making one nomination for each award.

Nominations for the Awards should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma. All nominations, accompanied by a statement of the importance of the nominee's contributions to endocrinology and a bibliography of his most important papers with reprints if possible, should be sent to Dr. Turner's office not later than March 15, 1948.

## THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. Edward A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori. No award was made in 1943. No age or special limitation is stipulated by the donor of the award.

## THE CIBA AWARD

The Ciba Award, established in 1942, is given in recognition of the meritorious accomplishment of an investigator, not over 35 years of age, in the field of clinical or pre-clinical endocrinology. In 1944 the Award was given to Dr. E. B. Astwood; in 1945 to Dr. Jane Anne Russell; in 1946 to Dr. Martin M. Hoffman and in 1947 to Dr. Choh Hao Li. The Award is for $1,200.00. If within two years of the date of the Award, the recipient chooses to use it to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00.

## THE AYERST, McKENNA & HARRISON FELLOWSHIP

The first award of the Ayerst, McKenna & Harrison Fellowship was given to Dr. Samuel Dvoskin in 1947. The fellowship was founded in order to encourage investigation in the field of endocrinology rather than as an award

for work done. The amount of the fellowship is $2,500.00 annually. The nominee must possess the degree of Doctor of Philosophy or Doctor of Medicine or their equivalent. It is suggested that no restriction be placed on age, but that preference be given to applicants who have recently completed the requirements for their Ph. D. or M. D. degree. The nominee must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals; submit a program of proposed study; indicate one or more institutious where the proposed program will be carried out; submit statement of approval from the investigators with whom he proposes to conduct his research; serve full time if awarded a fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

## AMERICAN ASSOCIATION FOR THE STUDY OF GOITER

### VAN METER PRIZE AWARD

The American Association for the Study of Goiter again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Toronto, Canada, May 6th, 7th, 8th, 1948 providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double spaced copy sent to the corresponding secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia not later than February 1st, 1948. The committee, who will review the manuscripts, is composed of men well qualified to udge the merits of the compet ng essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author if it is possible for him to attend. The essay will be published in the annual Proceedings of the Association. This will not prevent its further publication, however, in any Journal selected by the author.

T. C. Davison,
*Corresponding Secretary*